# Estimating the prevalence of vitamin B12 deficiency in elderly population (older than 60 years) with dementia presenting to a tertiary care hospital

**A Dissertation submitted in partial fulfillment of**

**M.D (General Medicine) branch I Examination of the Tamil Nadu**

**Dr. M.G.R. UNIVERSITY, CHENNAI**

**To be held in 2008.**

# ESTIMATING THE PREVALENCE OF VITAMIN B12 DEFICIENCY IN ELDERLY POPULATION WITH DEMENTIA PRESENTING TO A TERTIARY CARE HOSPITAL

# C E R T I F I C A T E

This is to certify that the dissertation entitled "Estimating the prevalence of vitamin B12 deficiency in elderly population (older than 60 years) with dementia presenting to a tertiary care hospital" is the bonafide original work of Dr.Lijo Varghese towards the M.D. Branch- I (General Medicine) Degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai to be conducted in 2008.

Signature:

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# C O N T E N T S

# LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| **AD** | : **Alzheimer's Disease** |
| **B12** | : **Vitamin $B_{12}$** |
| **Cbl** | : **Cobalamin** |
| **CBC** | : **Complete Blood Counts** |
| **CDR** | : **Clinical Dementia Rating scale** |
| **CT** | : **Computed Tomography** |
| **CVA** | : **Cerebro Vascular Accident** |
| **DM** | : **Diabetes Mellitus** |
| **DSM** | : **The Diagnostic & Statistical Manual of Mental Disorders** |
| **DLBD** | : **Diffuse Lewy Body Dementia** |
| **ELISA** | : **Enzyme Linked Immuno Sorbent Assay** |
| **FA** | : **Folic acid** |
| **FTC** | : **Free Thyroid Concentration** |
| **FTD** | : **Frontotemporal Dementia** |
| **HB** | : **Hemoglobin** |
| **HC** | : **Homocysteine** |
| **HIV** | : **Human Immunodeficiency Virus** |
| **HTN** | : **Hypertension** |
| **IF Ab** | : **Intrinsic factor antibody** |

**IHD** : **Ischemic Heart Disease**

**LDH** : **Lactate Dehydrogenase**

**MCV** : **Mean Corpuscular Volume**

**MMA** : **Methylmalonic acid**

**MMSE** : **Mini Mental State Examination**

**MRI** : **Magnetic Resonance Imaging**

**NINDS** : **National Institute of Neurological Disorders and Stroke**

**NPH** : **Normal Pressure Hydrocephalus**

**PA** : **pernicious anemia**

**PBS** : **Peripheral Blood Smear**

**PDD** : **Parkinson's disease with dementia**

**PLT** : **Platelets**

**SDH** : **Subdural Hematoma**

**T4** : **L- thyronine concentration**

**T.B/D.B** : **Total bilirubin / Direct Bilirubin**

**TC** : **Total white blood cell Count**

**THF** : **Tetrahydro Folate**

**TSH** : **Thyroid Stimulating Hormone**

**VaD / M.I.D** : **Vascular Dementia / Multi Infarct Dementia**

**VDRL** : **Venereal Diseases Research Laboratory**

# A I M OF THE STUDY

The aim of our study was to determine the prevalence of major types of dementia in our population and to specifically look at the prevalence of B12 deficient dementias.

# OBJECTIVES OF STUDY

1) To determine the causes of dementia in elderly patients (>60 years) and to estimate the prevalence of dementia due to vitamin B12 deficiency, in patients presenting to a tertiary care hospital.
2) To assess the profile of B12 deficient patients in terms of clinical presentation, laboratory correlates and diet.
3) To calculate the mean MMSE scores among the various dementia categories and assess any difference in the pattern of dementia.
4) To assess the improvement in MMSE after administration of injection B12 in those with vitamin B12 deficiency.
5) To study common risk factors of vascular dementia in our population.

# I N T R O D U C T I O N

Dementia is defined as an acquired impairment of memory and intellectual functioning, which is not associated with fluctuations in the level of consciousness.[1] It must be differentiated with delirium which has a different set of causes.

Dementia is a common problem in the elderly with the prevalence increasing with age and approaching 40% in patients above 80 years of age. It is a major cause of morbidity in the elderly. With the increasing life expectancy in India (currently 65 years), we can expect to encounter more and more cases of dementia. The vast majority of cases of dementia are degenerative or vascular in nature and are usually relentlessly progressive with few therapeutic measures for treatment available. Hence the importance of detecting the reversible causes of dementia.

There are only a few reversible causes of elderly dementia of which vitamin B12 deficiency is the most easily treatable one. It is well known that B12 deficiency can cause isolated dementia and that it can be a coexisting factor in other irreversible dementias.

Hence this study focuses on studying the prevalence of various types of dementia in the elderly population presenting to a tertiary care hospital in South India and specifically looking at the prevalence of B12 deficiency and studying the profile of B12 deficient patients. We also aim to look at the risk factor profile of patients with vascular dementia, which is the most common cause of dementia in our setting.

# L I T E R A T U R E  R E V I E W

## EPIDEMIOLOGY

*** THE ELDERLY POPULATION:**

The world's elderly population is currently growing at 2.4% per year, considerably faster than the global population. In developed countries, the present elderly population numbers 165 million and is projected to expand to 257 million by 2025. Sweden with 17.5% of its population being more than 65 years has the highest proportion of elderly people. By the year 2025, 68% of the world's population aged 65 and above, nearly 277 million people, will be residing in developing countries.[2]

The current median age (number of people under and over this particular age is equal) in developed countries is 35 years.

The average life expectancy is highest in Japan reaching 80 years and women on an average live 5-7 years more than their men counterparts.

In India, the percentage of people above 60 years of age was 5.9 and 7.2 in 1970 and 1995 respectively. This is expected to rise up to 11% by 2020. [2]

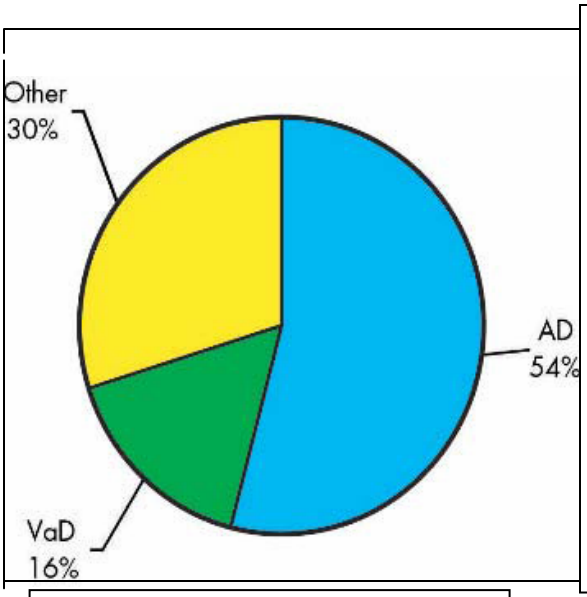



FIGURE A:Causes of dementia with late onset (> 65 years). Based on Lobo et al. (Europe) [3]

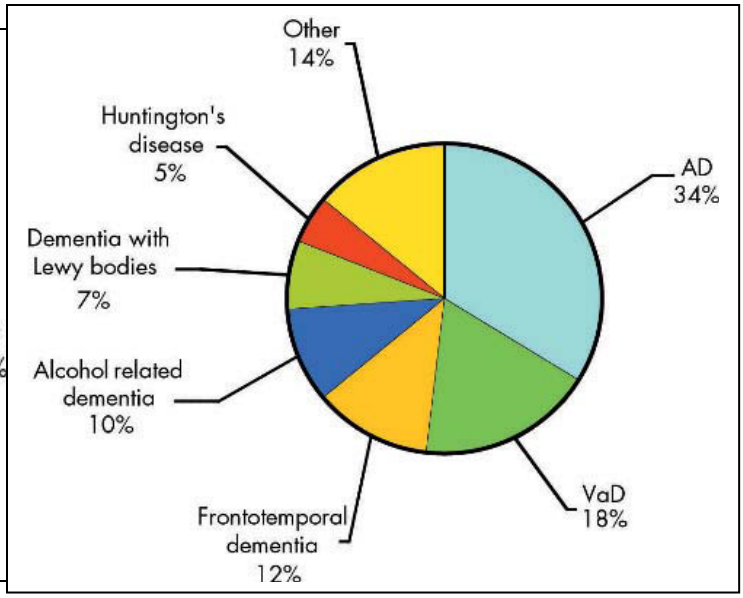



FIGURE B: Causes of dementia with young onset (, 65 years). Based on Harvey et al (USA) [4]

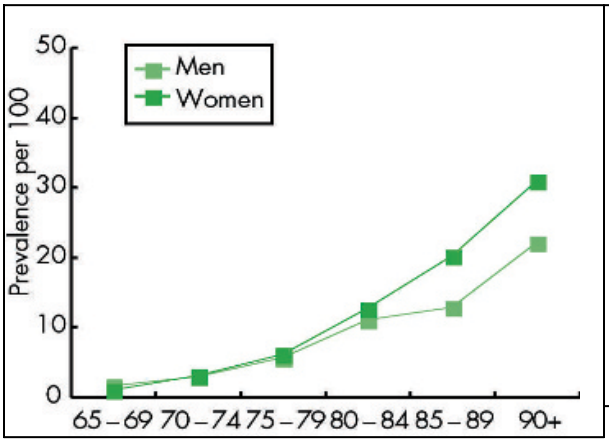



FIGURE C: Pooled prevalence of dementia by sex. Based on Lobo et al. [3]

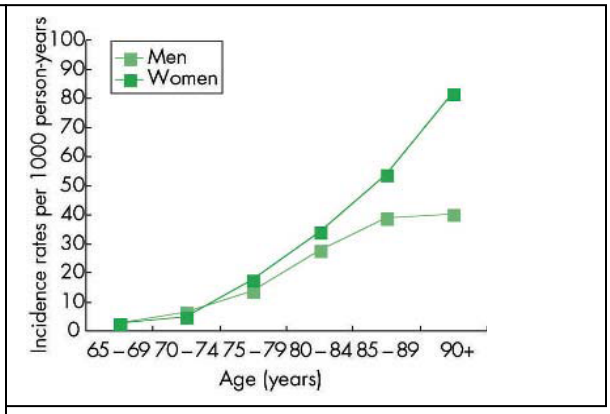



FIGURE D: Pooled incidence rates of dementia by sex. Based on Fratiglioni et al. [5]

*** EPIDEMIOLOGY OF DEMENTIA:**

The prevalence of dementia **doubles every 5 years of life after the age of 65** worldwide. The total number of people with dementia in the world was 11 million in 1980, 18 million in 2000 and is likely to be 34 million in 2025.[2]

In the **US**, the commonest type of dementia in elderly is **Alzheimer's** (**55%**), followed by Vascular dementia (**20%**), Diffuse Lewy Body Dementia (**15%**), Fronto-temporal dementia (**10%**). [Data from The Alzheimer's USA Society, 2000 update]. But in Japan, Russia, China and India, vascular dementia is the commonest cause.

As shown in the figures on the left side the causes of dementia vary in different age groups and in the >80 year group, Alzheimer's and multi-infarct attribute to majority of dementias. Also figure C & D and table A show a higher prevalence of dementia in women with increasing age. Same trend is seen in Alzheimer's and vascular dementias.

WORLD WIDE PREVALENCE OF DEMENTIA - BURDEN OF DISEASE**:**

In the **US** study by ***Ganguli et al*** [6], in Pittsburgh, to determine the overall prevalence of AD, it was found that the prevalence significantly increased with age as follows- 1% for 55-69 years, 3% for 70-79 years, 15.7% for 80-85 years and 25% for >85 years. The latest figures report upto 40% prevalence in those >85 years. [The Alzheimer's USA Society].

In **UK**, the prevalence of dementia is 2%, 10% and 33% for those aged between 60-70 years, 70-80 years and >80 years respectively. Currently there are an estimated

700,000 people with dementia in U.K and this is expected to rise to 840,000 by 2010 and to 1.5 million by 2050. [The Alzheimer's UK Society].

INCIDENCE OF ALZHEIMER'S DISEASE (AD):

The **incidence** of AD in Europe & US is 0.5% at 65 yrs, 1% at 70, 2% at 75, 3% at 80. The incidence rate is 14 times higher for those aged 85 than those aged 65.[7].

VASCULAR DEMENTIA: (VaD)

The overall prevalence of vascular dementia is 5.6% in people older than 60 years. The prevalence ranges from 2.2% in 70- to 79-year-old women, to 16.3% in men >80 years. VaD had an increasing prevalence with age (a doubling every 5.3 years).

In Europe, the prevalence of vascular dementia is estimated to be 1.5-4.8% for individuals between the ages of 70 and 80 years old. A Swedish study estimated the lifetime risk of VaD as 34.5% for men and 19.4% for women [8].Dementia was diagnosed in 26.3% and 31.8% of patients, respectively, in two studies at three months after an acute stroke[9] . Within 4 years following a stroke, the relative risk of incident dementia is 5.5% [10].

The annual incidence rates of VaD (per 100,000) range from 20 to 40 between 60 and 69 years of age and from 200 to 700 over 80 as per the Dutch Vascular Study.[11] In community-based studies in Europe, the incidence of VaD has ranged from 0.17 to 0.71 per 100 person-years[12]. In a sample of hospitalised ischaemic stroke patients, the incidence of VaD was estimated to be 8.4 per 100 person-years[13]

**Table A: EURODEM meta-analyses of dementia for European studies**: [14]

| AGE GROUP | ANNUAL INCIDENCE (/100) | | PREVALENCE (%) | |
|---|---|---|---|---|
| | MALE | FEMALE | MALE | FEMALE |
| 60-64 | 0.2 | 0.2 | 0.4 | 0.4 |
| 65-69 | 0.2 | 0.3 | 1.6 | 1.0 |
| 70-74 | 0.6 | 0.5 | 2.9 | 3.1 |
| 75-79 | 1.4 | 1.8 | 5.6 | 6.0 |
| 80-84 | 2.8 | 3.4 | 11.0 | 12.6 |
| 85-89 | 3.9 | 5.4 | 12.8 | 20.2 |
| >90 | 4.0 | 8.2 | 22.1 | 30.8 |

PREVALENCE IN DEVELOPING COUNTRIES & INDIA:

However, in the developing world there is more uncertainty about the frequency of dementia, with few studies and widely varying estimates. In general, both prevalence and incidence are lower than in the developed world (10/66 Dementia Research Group, 2000). Less than one tenth of all population-based research into dementia has been directed towards the two-thirds or more of all people with dementia who live in developing parts of the world. Hence "10/66". [15]

By 2025, there will be twice as many people with dementia in the developed world & **four times** as many people with dementia in the developing world as there were in 1980. By 2025, **71%** of people with dementia will live in developing countries.[2]

As compared to higher prevalence of dementia in developed countries ranging between 5-10% after 60 to 65 yr of age, several urban and rural studies on dementia from different parts of India had documented lower rates varying from **1.02 to 3.36%** above 60 to 65 yr of age as shown in the following studies which specifically looked at the prevalence of dementia in rural and urban populations.

In a study done by ***RajKumar et al*** in **Chennai** [16] , the prevalence of dementia in >60 years was **3.5%** and increased with age.

In another study done by ***Verghese et al*** [17] in a **rural** community in **Kerala**, the prevalence rate of dementia was **3.2%**. 58% were vascular dementia and 40% were Alzheimer's. Another study done by the same group in an **urban Kerala** population [18] showed a prevalence of **3.4%** and here the most common cause was Alzheimer's (54%) followed by vascular dementia (38%).

In a similar Urban study done in **Mumbai** by ***Pinto et al***, the prevalence of dementia in the elderly was **2.44%** and that of Alzheimer's was 1.5%. [19]

The study by ***Ganguli et al***, [6] from the Indian subcontinent, showed a very low prevalence of AD in Ballabgarh, (rural) India, but association of APOE*E4 with AD was similar in Indian and US samples. The frequency of probable or possible AD, with Clinical Dementia Rating score of at least 1.0, in the Indian vs US samples, was as follows: aged 55 to 69 years, 0.1% (Indian sample only); aged 70 to 79 years, 0.7% vs 3.1%; aged 80 years or older, 4.0% vs 15.7%. The authors say that shorter follow up, cultural factors and smaller life span could have been contributory factors for lower prevalence in India.

## DEMENTIA SYNDROMES [20,21]

*** IRREVERSIBLE CAUSES**

- Alzheimer's disease (AD)
- Dementia with Lewy bodies (DLB)
- Fronto temporal dementia (FTD)
- Vascular (multi-infarct) dementia (VaD)
- Parkinson's disease with dementia (PDD)

*** REVERSIBLE CAUSES**

- Alcohol-related (eg, intoxication, withdrawal)
- Metabolic disorders (eg, thyroid disease, vitamin B12 deficiency, hyponatremia, hypercalcemia, hepatic and renal dysfunction)
- Depression (pseudodementia)
- CNS tumors, chronic subdural hematoma, chronic meningitis
- Normal pressure hydrocephalus

**EPIDEMIOLOGY OF REVERSIBLE CAUSES:**

The reversible causes of dementia form an important component of all dementias. The most important are B12 deficiency, normal pressure hydrocephalus and metabolic causes including drug induced dementia. Among these, B12 deficiency is the most easily treatable cause. Hence it is important to know the risk factors and clinical profile of B12 deficient patients. Also there are some clinical features which can differentiate a reversible from irreversible cause, which are mentioned later under this section.

Most of the studies have been done on Alzheimer's and there are not many studies addressing the reversible causes of dementia, though the prevalence may vary from **5-37%** as demonstrated in the following studies.

In the largest and earliest single study by ***Hejl et al*** [22], 1000 pts referred to a university hospital were prospectively evaluated to assess the prevalence of dementia based on etiology. The mean age at enrolment was 66 yrs (range 17 to 98), and 43% met the diagnostic criteria for dementia. A potentially reversible primary etiology for the cognitive symptoms was identified in **19%**. Depression was the most common primary etiology (9.8%), followed by hydrocephalus and alcohol dependence syndrome (3.4 & 1.9%, respectively). The prevalence of a potentially reversible cause was higher in younger (<60 years) than in older patients (28 versus 14%).

There are 2 prominent meta-analyses done recently:

1) A meta-analysis of 32 studies including 2889 patients [23] (mean age 72 years) found that **13%** of patients had a potentially reversible cause. The most common reversible causes in this report were drugs (28%), depression (26%), and metabolic diseases (16 percent). A 2003 update of the above meta-analysis found 39 studies including 7042 patients and concluded that the prevalence of reversible dementias is decreasing. Potentially reversible causes were seen in only **9%** of cases. [24]

2) A quantitative review of 16 studies (1551 patients) found that the frequency of potentially reversible dementia varied widely from **0 to 37.5%**. [25].

## DURATION OF DEMENTIA IN REVERSIBLE CAUSES:

In the Indian study by ***Nagaraja et al*** [26] in **Karnataka**, the commonest type of dementia was Alzheimer's (54%) followed by vascular (25%) and then reversible causes (18%). The average duration of dementia was 30, 15 and 15 months respectively in the 3 groups. In a study from **Washington** university [27], the duration of reversible causes was 28 months and irreversible causes was 50 months. Hence from both above studies, it is clear that **reversible dementias have a shorter duration** at presentation.

## CLINCAL DIFFERENCE BETWEEN REVERSIBLE & IRREVRSIBLE CAUSES

The study by ***Nagaraja et al*** [26] found that the following factors favoured a reversible cause:

- younger age of onset
- **shorter illness duration**
- **moderate cognitive subcortical** dementia
- **psychiatric** disturbance
- gait disturbance and urinary dysfunction
- focal neurological signs. Bilateral pyramidal signs & extrapyramidal signs, however, favoured irreversible causes.

The average MMSE for reversible dementia was **18** and for irreversible was 15 (p=0.01) in this study. In the study ***Larson et al***,average MMSE in irreversible causes was 14 & in reversible causes was **20.** [27]

Most reversible causes result in a subcortical pattern of dementia whereas irreversible causes have a cortical pattern. The "cortical dementias" (exemplified by Alzheimer disease)are distinguished by more severe disturbances of memory, language, and calculation, prominent signs of apraxia and agnosia, and impaired capacity for abstract thought (this is illustrated in table B below). [28]

Table B: Clinical features differentiating cortical & subcortical dementias: [28]

| Features/Dementia type | **SUB-CORTICAL** | **CORTICAL** |
|---|---|---|
| **Severity** | Mild to moderate | severe |
| **Speed of cognition** | slow | normal |
| **Neuropsych deficit** | Frontal & memory impairment | Dysphasia, Dyspraxia,Agnosia |
| **Neuropsych symptom** | Apathy, depression | lesser |
| **Motor** | Dysarthria, EPS | lesser |
| **Pathology** | Changes in thalamus & stratum | cortex |
| **Example** | Progr Supranucl palsy, B12 def | Alzheimer's |

## VITAMIN B12

There are only a few reversible causes of dementia in the elderly of which Vitamin B12 deficiency is the most easily treatable one. Vitamin B12 deficiency can cause isolated dementia or can be a coexisting factor in other irreversible dementias.

### EPIDEMIOLOGY OF B12 DEFICIENCY AND DEMENTIA:

Many studies report a variable incidence of B12 deficiency causing dementia.

### {A} WORLD WIDE PREVALENCE:

In the first study done in US, out of total of 181 consecutive, outpatients with dementia (score below 24 on the MMSE), the frequency of vitamin B12 deficiency (less than 200 pg/mliter) was **25%** (46 pts) [29].

. In another retrospective study from the Bristol Clinic involving 1432 patients with neuropsychiatric symptoms, dementia was present in 66 of which **1/3$^{rd}$** was B12 deficiency related.[30]. A study from UK [31] in elderly found that the prevalence of B12 deficiency increased with age- 5% in 65-74 years age group to 10% in >75 years.

Another important fact was that many patients had B12 deficiency associated with either Alzheimer's or vascular dementia. Consequently such patients had **more severe memory loss and lesser reversibility** with administration of B12. Increased levels of homocysteine associated with low vitamin B12 levels were found in AD patients. This observation led to consider that that neuronal damage results in a functional vitamin B12 deficiency even in Alzheimer's patients.[32].

**{B} PREVALENCE IN INDIA:**

The data for B12 deficiency and elderly patients with dementia seems to be limited to a handful of studies in India. B12 deficiency is more common in North India whereas folate deficiency is common in South and East India. [33]

In Yajnik's study from Pune, 67% and 80% of men in rural and urban middle class, respectively, had low vitamin B12 concentration (<150 pmol/L) [34] and 60% of rural women had low B12 [35]. These patients were randomly selected and many did not have any clinical manifestations of B12 deficiency.

The first major study which looked into various causes of dementia in elderly (>60yrs) in India was from **SGPGI** hospital [36]. It was a prospective study conducted on 124 (94 male and 30 female) elderly patients (aged more than 60 years) presenting with clinical syndrome of dementia (MMSE less than 24). Their age range was 64-78 (mean 65.7 4.1) years. Multi-infarct dementia (MID) was observed to be commonest cause of dementia and was present in 59 (47.6%) cases followed by,10 (8%) patients each of tuberculosis (TB) and neurocysticercosis (NCC), Alcohol-related dementia in 13 (10.5%),malnutrition (Vitamin B12 deficiency) was present in 9 (**7.2%**), AD in 6 patients (4.8%),1 each of Huntington's disease, Parkinson's and Normal Pressure Hydrocephalus and 2 each of diabetes, hypothyroidism, hyperthyroidism and Creutzfeldt' Jakob Disease. It was concluded that AD, which is irreversible and common in the west, is relatively uncommon in India as compared to M.I.D, infections and malnutrition, which are potentially treatable. The other study which suggested a very low prevalence of AD in India was by Ganguli et al as mentioned earlier.

In a prospective 3 year study from Neurology department **CMC, Vellore**, [37] to evaluate neurological manifestations of B12 deficiency in 63 patients (52 males), the mean duration of symptoms at presentation was 10.3 months. Neuropsychiatric manifestations and dementia were observed in 38% and **19%** of patients respectively Myeloneuropathy (54%) was the commonest neurological manifestation, followed by myeloneuropathy with cognitive dysfunction (34%), and peripheral neuropathy (9%).. All the patients had megaloblastic changes in the bone marrow smear. 11 (17.5%) patients had both hemoglobin and the mean corpuscular volume (MCV) within the normal range due to concomitant iron deficiency.

A study from **AIIMS** [38] recorded serum B12 levels in 100 patients. None of these patients were noted to have any clinical features suggestive of classical cobalamin deficiency. The significantly lower B12 mean concentrations in the Alzheimer's group compared to other dementias indicated that Alzheimer's patients are particularly prone to cobalamin deficiency. The exact reason for this is not known and has led to cobalaminergic hypothesis for Alzheimer's.

**{C} VEGETARIANISM & $B_{12}$ DEFICIENCY IN INDIA:**

In ***Yajnik's*** study from Pune, in rural non-pregnant vegetarian women,reported that oral B12 supplements (as tablets or vegetables) increased the B12 levels from 125 to 215 pmol/L and reduced the homocysteine concentration from 18 to 13 micromol/L. [35]

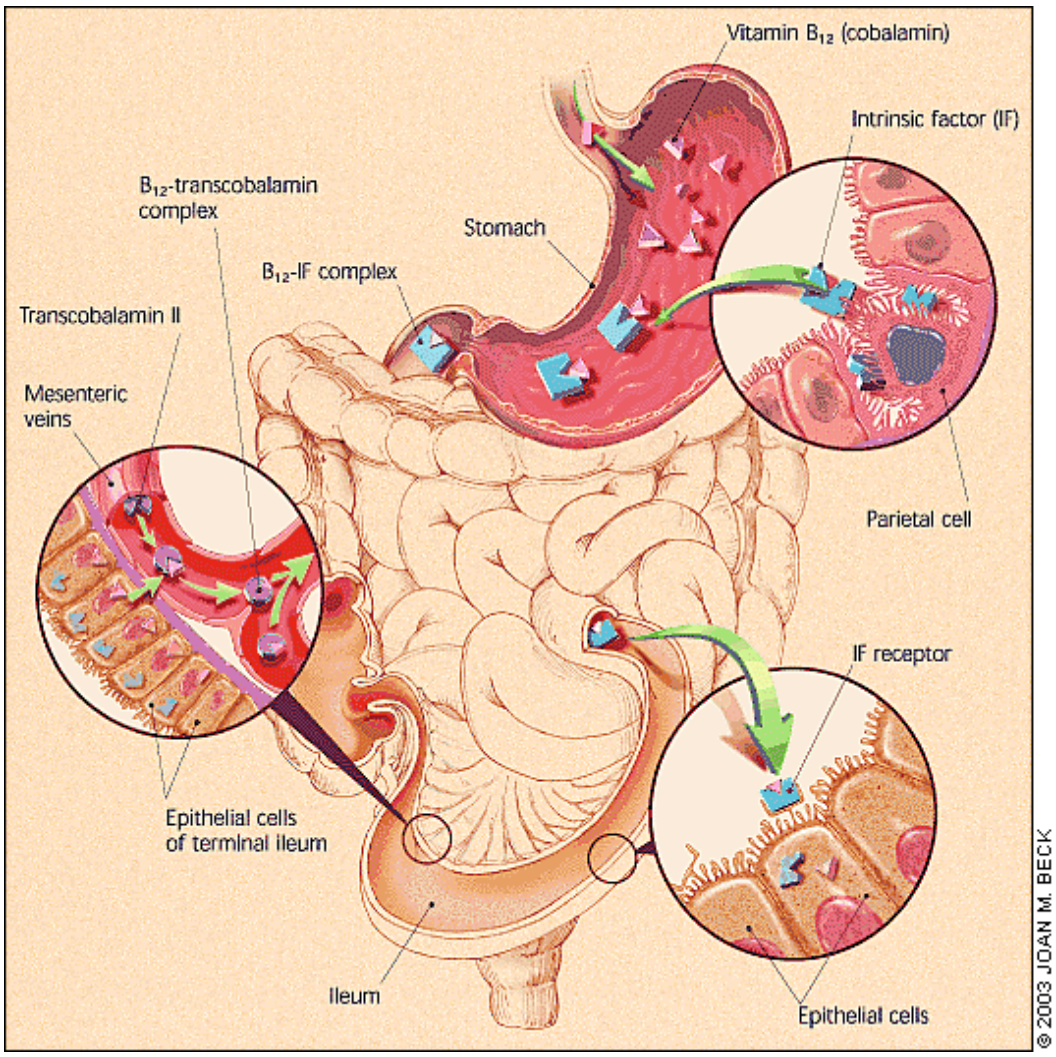
In Yajnik's second study from Pune in rural and urban men, Vegetarians had 4.4 times (95% CI 2.1, 9.4) higher risk of low vitamin B12 concentrations and 3.0 times (95% CI 1.4, 6.5) higher risk of hyperhomocysteinemia compared to those who ate non-vegetarian foods frequently. [34]

**CAUSES OF B12 DEFICIENCY:** [39,40]

Table C: Causes of vitamin B12 deficiency:

| | |
|---|---|
| GASTRIC ABNORMALITIES: Pernicious anemia, Gastrectomy, Atrophic gastritis, Autoimmune conditions | SMALL INTESTINE DISEASE: : Malabsorption syndrome, Ileal resection or bypass, Crohn's, Blind loops, Pancreatitis |
| DIET: Strict vegans | DRUGS: Neomycin, Metformin, Proton Pump Inhibitors(PPI), Nitric Oxide |

Figure E: Absorption & transport of $B_{12}$:



**ABOUT B12 AND ITS ABSORPTION:**

Animal products (meat and dairy products) provide the only dietary source of cobalamin (Cbl) for humans. The usual western diet contains 5 to 20 micrograms of cobalamin per day, while the minimum **daily requirement** is listed as **6 to 9 micrograms per day**. Total body **stores of Cbl are 2 to 5 milligrams**, approximately one-half of which is in the liver. As a result, actual vitamin B12 deficiency develops many years after absorption of dietary B12 ceases [41,42].

The absorption of B12 is shown in figure E. The acidic environment of the stomach facilitates the breakdown of vitamin B12 that is bound to food. Intrinsic factor, which is released by parietal cells in the stomach, binds to vitamin B12 in the duodenum. This vitamin B12-intrinsic factor complex subsequently aids in the absorption of vitamin B12 in the terminal ileum. Once absorbed, vitamin B12 binds to transcobalamin II and is transported throughout the body. The interruption of one or any combination of these steps places a person at risk of developing deficiency

Absorption of Cbl depends upon **five factors**: [43,44,45]

- Dietary intake
- Pepsin in the stomach to liberate Cbl from its protein bound state
- Pancreatic proteases to cleave Cbl from R factors
- Secretion of intrinsic factor (IF) by the gastric parietal cells which bind to Cbl
- A functional ileum with Cbl-IF receptors.

**ELDERLY AND B12 DEFICIENCY:**

Mild, and usually subclinical cobalamin deficiency appears to occur (or be recognized) with increased frequency (10 to 24%) in the elderly [46].

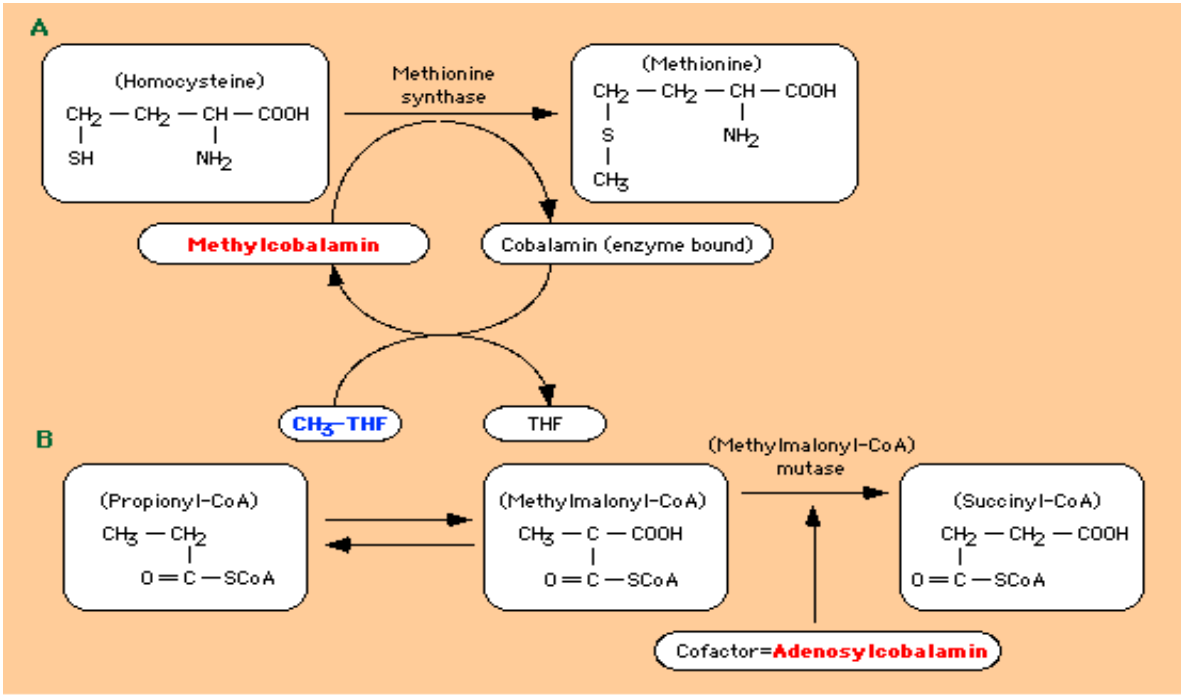
PREVALENCE OF B12 DEFICIENCY IN ELDERLY:

In a population-based cross-sectional analysis of 3,511 elderly people from the UK, the age-specific prevalence of cobalamin deficiency was approximately **5 and 10%** in those age 65 to 74 and those more than 75 years of age, respectively, and majority of them had dementia [47]. In a series of 107 healthy, free living Dutch subjects between the ages of 74 and 80, **24%** had evidence of mild cobalamin deficiency [48]

Factors that contribute to cobalamin malabsorption in the elderly include [49]:

- Gastric atrophy, achlorhydria , pernicious anemia
- *Helicobacter pylori* infection
- Intestinal bacterial overgrowth secondary to antibiotics
- Chronic intake of biguanides, antacids, $H_2$ receptor antagonists, and PPIs.
- Chronic alcoholism
- Gastric surgery or reconstruction for obesity , ileal resection
- Pancreatic exocrine failure and Crohn's (cause malabsorption)

Figure F: 2 major reactions involving Vitamin $B_{12}$:




Taken from- Biochemical Basis of Cobalamin Deficiency. Mayo Clinic 1994

**PHYSIOLOGICAL ROLE OF VITAMIN B12:**

Cbl has 2 known cofactor actions: [50] as shown in figure F

{A}Conversion of propionyl-Co Acetate (CoA) to methylmalonyl CoA and finally to succinyl-CoA. There is no interaction with FA in this pathway; as a result, it has been proposed that this pathway might be important in myelin formation and in the neurologic abnormalities seen with B12 but not FA deficiency.

{B}Transfer of a methyl group from methyl tetra hydro folate (THF) via Cbl to homocysteine to form methionine - this reaction has 2 important effects: it reduces the plasma concentration of homocysteine which is probably toxic to endothelial cells; and it demethylates THF. Demethylation is a critical step in DNA synthesis because THF (the reduced form of folate) and not methyl-THF is the substrate for the enzyme that converts (THF)-1 to the polyglutamated form, (THF)n.

**MANIFESTATIONS OF VITAMIN B12 DEFICIENCY:**

Deficiency of both cobalamin and folic acid produce megaloblastic anemia but only B12 deficiency produces neurologic changes. The classic picture of cobalamin deficiency due to pernicious anemia was that of a prematurely gray woman of Northern European descent who was lemon colored (reflecting anemia and icterus), mentally sluggish, had a shiny tongue (atrophic glossitis) and a shuffling broad gait. [51]

The neuropsychiatric manifestations of vitamin B12 deficiency are : [52]

**1)Autonomic** - Impotence, urinary or fecal incontinence

**2)Cerebral** - Dementia, depression, memory loss, psychosis, cerebrovascular disease (through high serum homocysteine levels)

**3)Myelopathic -** ataxia, spasticity, and abnormal gait

**4)Myeloneuropathic** - Combined myelopathy and neuropathy, Subacute combined degeneration

**5)Neuropathic** - Peripheral sensory and motor neuropathy (paresthesias, numbness, weakness), mononeuropathy (optic or olfactory atrophy), Lhermitte's sign. Neuropathy affects 70% of patients. Loss of vibration sense is early sign followed by loss of joint position sense

**6)Psychiatric** - B12 deficiency can cause depression, bipolar-1 disorder (manic depressive) and more commonly bipolar-2 (cyclothymic personality). Psychotic forms of depression have been particularly associated with B12 deficiency.

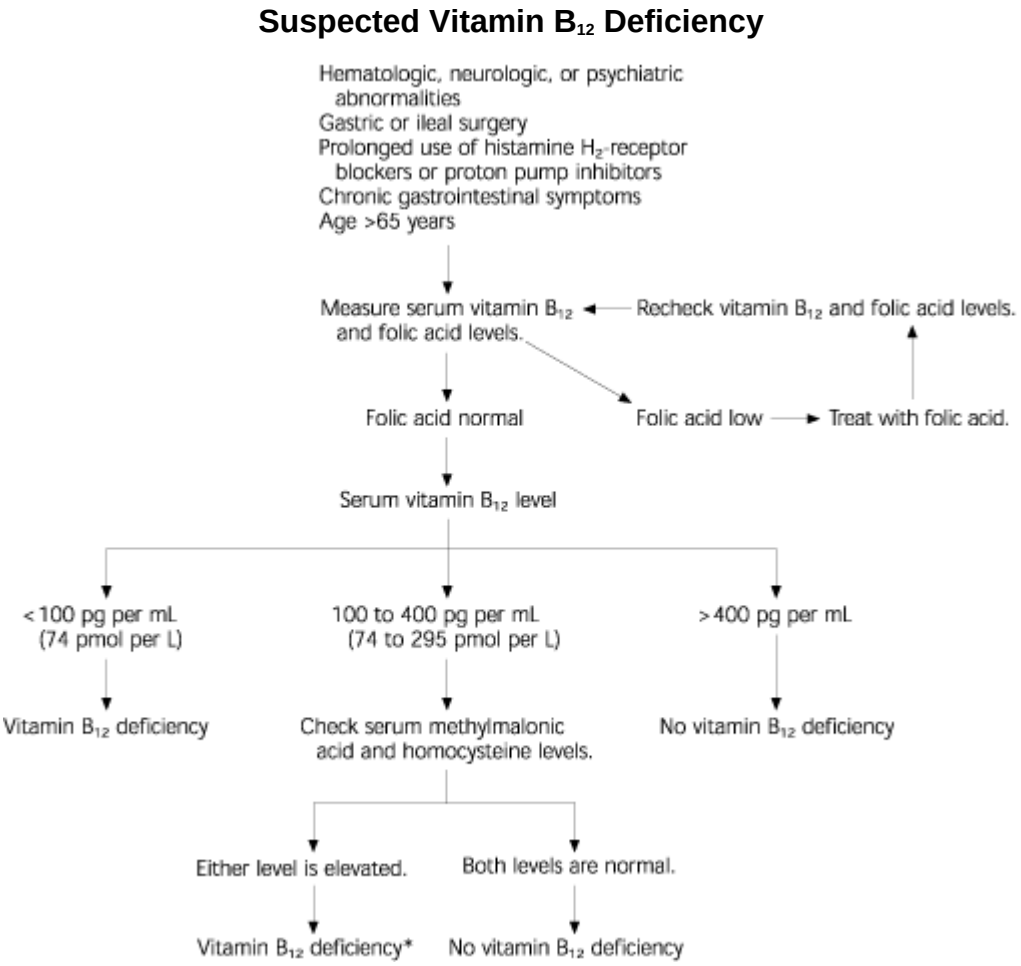
A small study suggests that there is a slight difference in the domain of memory and intelligence affected in B12 deficient patients when compared to other causes of dementia. 12 patients who showed good improvement with B12 treatment had initially more psychotic problems and more deficits in concentration, visuospatial performance, and executive functions. They did not show language problems and ideomotor apraxia, which were present in the other groups. Their memory pattern was also different. [53]

**LAB FEATURES OF B12 DEFICIENCY:**

**1) PERIPHERAL SMEAR -**

- The degree of elevation of the **MCV** is often a clue as to whether a vitamin deficiency is present. Thus, the probability of a deficiency of folate and/or Cbl being present when the MCV is 80 to 100 fl (normal), 115 to 129 (high), or >130 fL (very high) has been estimated at <25, 50, and 100 percent, respectively [54]. Unless a combined deficiency (eg, iron deficiency plus a deficiency of Cbl and/or folate) is suspected, routine testing for Cbl or folate deficiency in an anemic patient in the presence of a MCV <80 fL is not likely to be productive.
- Peripheral pancytopenia
- Macroovalocytes, hypersegmented neutrophils (earliest change), basophilic stippling, occasional megaloblast
- Elevated bilirubin and LDH due to ineffective erythropoiesis.

Figure G: Approach to B12 Deficiency:

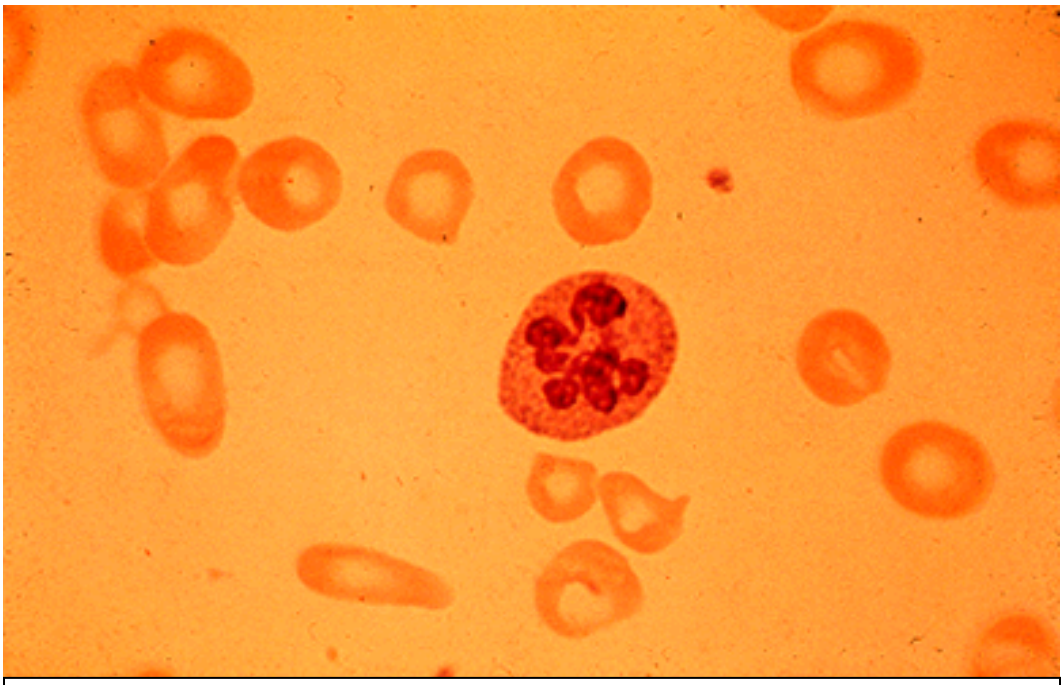


**2) B12 LEVELS –**

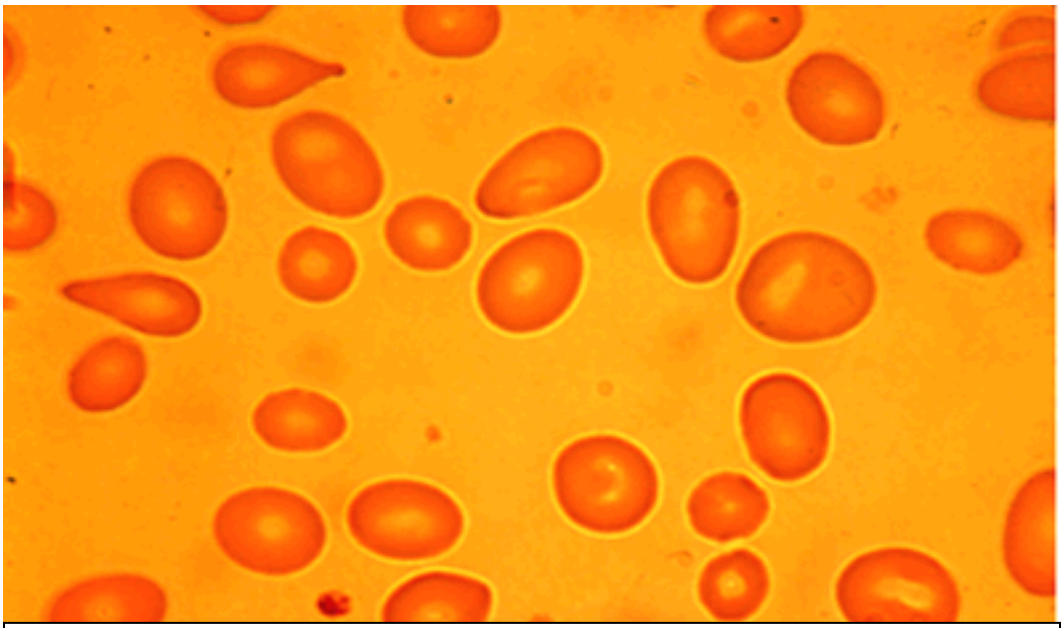
Several commercial laboratories use different methods (chemiluminescence or radioassay) for measuring Cbl. As a result, there are different normal ranges and no "gold standard" [55]. B12 deficiency can be classified, based on serum levels, as [56,57,58]:

- **>300** pg/mL (>221 pmol/L) — **normal**; Cbl deficiency is unlikely.(ie,1 to 5%)
- **200 to 300** pg/mL (148 to 241 pmol/L) — **borderline**; Cbl deficiency possible
- **<200** pg/mL (<148 pmol/L) — **low**; consistent with Cbl deficiency(specificity of 95-100%). However U.S.clinical laboratories regard 200 pg/ml as the lower range of normal.

The serum Cbl concentration may be normal in up to 2-5% of patients with documented Cbl deficiency. One possible explanation for vitamin B12 deficiency with only borderline subnormal vitamin B12 serum levels is the presence of cobalamin analogues that cause high vitamin B12 values in presently used assays with R-binders. Vitamin B12 levels may be falsely elevated in hepatic dysfunction and myeloproliferative disorders and falsely lowered in pregnancy [59], contraception usage and a low folate level. [60] Hence in such conditions and in those with borderline B12 levels (200-300pmol/L), it is advised to measure MMA or HC levels as shown in figure G or confirm by doing a marrow smear.



Peripheral smear showing hypersegmented neutrophil. Courtesy of Stanley L Schrier, MD. MAYO CLINIC



Peripheral smear shows marked macroovalocytosis in a patient with vitamin B12 deficiency. Courtesy of Stanley L Schrier, MD. MAYO CLINIC

**3) MEASUREMENT OF MMA AND HC –**

Serum concentrations of homocysteine (HC) and methylmalonic acid (MMA) are elevated in Cbl deficiency, due to a decreased rate of metabolism. In comparison, only HC is elevated in folate deficiency, since folate does not participate in MMA metabolism. As mentioned earlier, the measurement of the serum concentrations of HC and MMA is helpful in clarifying the diagnosis when serum Cbl or folate concentrations are equivocal [61]. In a study done in US [62] , elevated MMA & HC (3 SD above mean) had a sensitivity of **99.8%.**

**4) IF-ANTIBODY LEVELS-** The presence of anti-intrinsic factor (IF) antibodies is highly confirmatory for the diagnosis of pernicious anemia, with a sensitivity varying from 70 to 84 percent [63], depending upon the population tested, and a specificity approaching 100 percent. On the other hand, anti-parietal cell antibodies are much less specific, and may even be less sensitive (50%).[64]

**5) SCHILLINGS TEST-** reserved for those who are IF-Ab negative and done with radiolabelled cyano-cbl.[65]

**6) BONE MARROW EXAMINATION-** Bone marrow aspiration and biopsy reveal a very hypercellular marrow with megaloblastic erythroid hyperplasia and giant hypersegmented metamyelocytes due to inadequate conversion of deoxyuridate to thymidylate, which leads to slowing of DNA synthesis and delayed nuclear maturation.

**TREATMENT OF B12 DEFICIENCY:**

Pernicious anemia (PA) is typically treated with parenteral (ie, intramuscular) Cbl, in a dose of 1000 µg (1 mg) every day for one week, followed by 1 mg every week for four weeks and then, if the underlying disorder persists, as in PA, 1 mg every month for the remainder of the patient's life. Oral [66], sublingual [67] and nasal [68] preparations are available. With B12 treatment, MMA & HC levels fall in $B_{12}$ deficiency whereas MMA rises with only folate supplementation. Life threatening hypokalemia is a complication of B12 therapy.

**Schedule for Vitamin $B_{12}$ Therapy**

| Route of administration | Initial dosage | Maintenance dosage |
|---|---|---|
| Oral | 1,000 to 2,000 mcg per day for one to two weeks | 1,000 mcg per day for life |
| Intramuscular | 100 to 1,000 mcg every day or every other day for one to two weeks | 100 to 1,000 mcg every one to three months |

**PROGNOSIS AFTER TREATMENT:**

The greatest improvement occurs in those patients whose disturbance of gait has been present for less than 6 months. Recovery may be complete if therapy is instituted within a few weeks after the onset of symptoms. All neurologic symptoms and signs may improve, mostly during the first 3 to 6 months of therapy (upto 1 year), and then at a slower tempo, during the ensuing year or even longer. Most studies show that there is

some degree of improvement after treatment, although sometimes, in cases of longest duration (>1year), the best that can be accomplished is an arrest of progression.

In a study from Lebanon [69], to assess the improvement in cognition after B12 replacement found that after 12 months of treatment, 40 of 56 patients revealed cognitive improvement. **There was a prominent correlation between duration of cognitive symptoms and response to therapy**. Patients symptomatic for <12 months gained an average of six points on the MMSE (paired t test P = 0.0065), whereas patients symptomatic >12 months gained an average of four points (paired t test P = 0.25). Six patients symptomatic for only 3 to six months normalized their MMSE scores, gaining 1,2,3, 6, and 9 points, respectively. Similar reversibility is shown in other studies from UK [70] and US [71]. There are also other reports to suggest that supplementing B12 causes improvement in blood brain barrier and thus stabilizing cognitive functions. In a study by Wadia et al [72], out of 16 B12 deficient cases with MMSE of < 21, 6 improved markedly and 4 partially.

A review of 3 trials (De La Fourniere 1997; Hvas 2004; Seal 2002) showed no statistically significant evidence of a treatment effect of vitamin B12 supplementation on cognitive function. But these trials were restricted to a small number of patients with Alzheimer's disease and other types of cognitive impairment and had a short follow up. [73]. In a study from Bristol Clinic [30], 66 B12 deficiency dementia patients were identified and followed up 2 months after treatment. They found significant improvement in frontal lobe and language function in patients with cognitive impairment.

## DIAGNOSIS OF DEMENTIA :

### {A} DSM-IV CRITERIA FOR DEMENTIA: [74]

(Adapted from the American Psychiatry Association,1994)

Evidence from the history and mental exam, showing impairment in learning and memory, as well as at least one of the following:

- Impairment in handling complex tasks
- Impairment in reasoning ability
- Impaired spatial ability and orientation
- Impaired language

The cognitive symptoms must significantly interfere with the individual's work performance, usual social activities, or relationships with other people. This must represent a significant decline from a previous level of functioning. The disturbances must be of insidious onset and are progressive, based on evidence from the history or serial mental-status examinations. The disturbances must not occur exclusively during the course of delirium and not accounted for by a major psychiatric diagnosis, systemic disease or another brain disease.

**Additional criteria for dementia type:** [74]

**AD-** Gradual onset and continuing cognitive decline, not caused by identifiable medical, psychiatric, or neurologic condition

**VaD-** Focal neurological signs or laboratory evidence of cerebrovascular condition

**Miscellaneous-** Evidence from history, physical exam, or laboratory findings of a specific medical condition causing cognitive deficits (HIV disease, head trauma, Parkinson's disease, Huntington's chorea, Pick's disease, Creutzfeld-Jacob disease).

## {B} DSM-IV CRITERIA FOR ALZHEIMER'S:

DSM IV criteria for Alzheimer's has sensitivity & specificity of 76 & 80% respectively [75]:

- The gradual onset and continuing decline of cognitive function from a previously higher level, resulting in impairment in social or occupational function.
- Impairment of recent memory (inability to learn new information) and at least one of the following**:** disturbance of language; inability to execute skilled motor activities in the absence of weakness; disturbances of visual processing; or disturbances of executive function (including abstract reasoning and concentration).
- The cognitive deficits are not due to other psychiatric, neurologic, or systemic diseases.
- The deficits do not occur exclusively in the setting of delirium

## {C} CRITERIA FOR VASCULAR DEMENTIA:

Vascular dementia is the most common cause of dementia in India and South East Asia.

There are 2 main scoring systems for vascular dementia:

### 1) HACHINSKI'S ISCHEMIC SCORE:

This is one of the oldest scoring systems [76]

- Abrupt onset -2
- Stepwise deterioration -1
- Fluctuating course -2
- Nocturnal confusion -1
- Relative preservation of personality -1
- Depression -1
- Somatic complaints -1
- Emotional incontinence -1
- History of hypertension -1
- History of strokes -2
- Associated atherosclerosis -1
- Focal neurological symptoms -2
- Focal neurological signs -2

| |
|---|
| I<br>n<br>t<br>e |

**Maximal score** -18

**2) NINDS-AIREN CRITERIA** for probable vascular dementia: [77]

The criteria for the clinical diagnosis of probable vascular dementia include:

**Dementia**:

Defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.

**Exclusion criteria:** Cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.

**Cerebrovascular disease**:

Defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of no relevant CVD by brain imaging (CT or MRI) including multiple large vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white matter lacunes, or extensive periventricular white matter lesions, or combinations thereof.

(a) onset of dementia within three months following a recognized stroke;

(b) abrupt deterioration in cognitive functions; or a fluctuating, stepwise progression.

## SCREENING TOOLS FOR DEMENTIA:

**{A} MMSE** [78,79]– (FOLSTEIN, 1975) -takes 7 minutes to perform

*** ORIENTATION:**

- What is the date: (year)(season)(date)(day)(month)-1 point each - **5** points
- Where are we: (state)(county)(town)(hospital)(floor)- 1 point each - **5** points

*** REGISTRATION:**

Name three objects: one second to say each. Ask the patient all three after you have said them. Give one point for each correct answer. Then repeat them until he/she learns all three. Count trials and record. The first repetition determines the score, but if the patient cannot learn the words after six trials then recall cannot be meaningfully tested. Maximum score - **3** points.

*** ATTENTION & CALCULATION:**

Serial 7s, beginning with 100 and counting backward: one point for each correct; stop after five answers. Alternatively, spell WORLD backwards: one point for each letter that is in correct order. Maximum score - **5** points.

*** RECALL:**

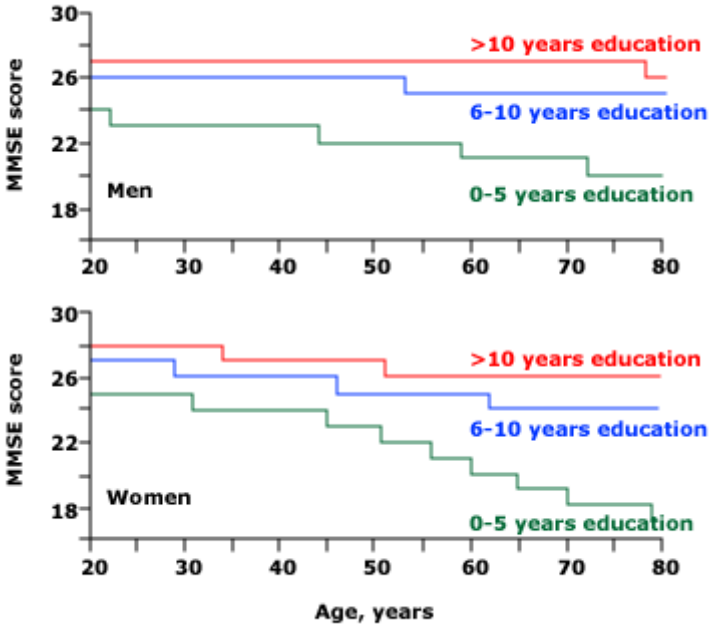
Ask for 3 objects repeated above: 1 point for each correct. Max score - **3** points

*** LANGUAGE & VISUAL RECONSTRUCTION:**

- Show and ask patient to name a pencil and wrist watch - **2** points
- Repeat the following, "No ifs ands or buts." Allow only one trial - **1** point
- Follow a three stage command, "Take a paper in your right hand, fold it in half, and put it on the floor." Score one point for each task executed. Max score - **3** points
- On a blank piece of paper write "close your eyes," and ask the patient to read and do what it says - **1** point
- Give the patient a blank piece of paper and ask him/her to write a sentence. The sentence must contain a noun and verb and be sensible - **1** point
- Ask him to reconstruct an intersecting pentagon – **1** point.

**MMSE SCORE INTERPRETATION:**

A total maximal score on the MMSE is **30** points. Generally a score of less than 24 points is suggestive of dementia or delirium. Using a cutoff of 24 points, the MMSE had a sensitivity of **87%** and a specificity of **88%** in a large population based sample [80]. However, the test is not sensitive for mild dementia, and scores may be influenced by age and education, as well as language, motor, and visual impairments [81].The use of higher cutoff scores on the MMSE improves sensitivity but lowers specificity. For research purposes, some investigators use a cutoff score of 26 or 27 in symptomatic populations in order to miss few true cases, while lower cutoffs could be necessary in populations where the expected prevalence is low [82]. Some groups have developed tools that incorporate age, gender, and education level as shown below: [83,84].




**MMSE GRADES AND MODIFICATIONS:**

Mild dementia-MMSE 21-24, mod- MMSE 15-20, severe- MMSE <14.[85]

The MMSE has been modified and translated into various languages. For example, in a study done by ***Mary Ganguli*** in India [86], the hindi version of MMSE, was validated and concluded that systematic, item-by-item, empirically based test development shows that effective modifications can be made to existing tests that require reading and writing; and that culturally sensitive modifications can be made to render the test meaningful and relevant while still tapping the appropriate cognitive domains.

For identifying dementia in a illiterate population, a combination of tests should be used as suggested in the Indo-US Epidemiological survey, in which, they used mental status test, the Hindi Mental State Examination (HMSE), and a brief neuropsychological test battery. [87]

| DIAGNOSTIC TEST | SENSITIVITY(PERCENT) | SPECIFICITY(PERCENT) |
|---|---|---|
| MMSE * | 87 | 88 |
| SHORT MMSE * | 80 | 78 |
| NINCDS ** | 90 | 65 |
| DSM-IV ** | 76 | 80 |
| CLINICAL JUDGEMENT ** | 80 | 75 |

* Diagnosis of dementia

** Diagnosis of Alzheimer's disease [88]

## OTHER BRIEF COGNITIVE ASSESSMENTS:

**{B} MINICOG**: consists of a clock drawing task (CDT) and an uncued recall of three unrelated word. The CDT is considered normal if all numbers are present in the correct sequence and the hands readably display the correct time. [89]

The advantages of the Mini-Cog include high sensitivity for predicting dementia status, short testing time relative to the MMSE, ease of administration, and diagnostic value not limited by the subject's education or language

**{C} INFORMANT INTERVIEW**: A brief, eight-item questionnaire for informants appears to be sensitive for detecting dementia and cognitive impairment. A positive response to >2 questions had a sensitivity of 93% and a specificity of 46%. Increasing the cutoff score to >3 positive responses decreased the sensitivity to 90% and increased the specificity to 68% [90].

**{D} SHORT PORTABLE MINI MENTAL QUESTIONNAIRE** : The short portable mental status questionnaire is another popular test of cognitive function. It can be performed in approximately five minutes. This test contains items that test orientation, attention, immediate recall, arithmetic, abstraction, construction, information, and delayed (approximately three minutes) recall. [91]

**{E} CLOCK DRAWING**: Asking the patient to draw a clock with a specific time is a quick examination that appears to correlate well with the MMSE score, although it has not undergone as rigorous an evaluation as the MMSE [92]. It is not a sensitive test for identifying very mild dementia [93].

## IRREVERSIBLE DEMENTIAS:

## {A}ALZHEIMER'S DISEASE:

Alzheimer's disease (AD) is a progressive neurologic disorder that results in memory loss, personality changes, global cognitive dysfunction, and functional impairments. Loss of short-term memory is most prominent early [94]. The pathology of AD, the presence of senile (neuritic) plaques and neurofibrillary tangles (NFTs), has been known since Alzheimer's investigations of his original patient in 1906 [95].

The proposed risk factors are advanced age, apoE ε4, family history of dementia, female sex, head injury, systolic hypertension, high fat diet and history of Myocardial infarction.

The ability to focus attention and recall remote events may be subtly impaired at first and always worsens with time. Progressive disorientation with respect to time and place is universal. The ability to perform activities of daily living, including driving, may be impaired by breakdowns of elemental visual-processing abilities and apraxia.

Personality changes range from progressive passivity to marked hostility and can develop before the cognitive impairments. Patients frequently show decreased emotional expression, increased stubbornness, diminished initiative, and greater suspiciousness. Delusions affect up to 50 percent of patients with Alzheimer's disease, and an early onset predicts rapid deterioration. Paranoid delusions are the most common type, leading to accusations of theft, marital infidelity, and persecution. Hallucinations, usually visual, occur in up to 25 percent of patients with Alzheimer's disease

## {B}VASCULAR DEMENTIA:

The identification of vascular dementias has suffered from a lack of uniform diagnostic criteria. [96,97] Features that **suggest the diagnosis** include:

- The onset of cognitive deficits associated with a stroke
- Abrupt onset of symptoms followed by stepwise deterioration
- Findings on neurologic examination consistent with prior stroke(s)
- Infarcts on cerebral imaging

Three common **pathological entities** contribute substantively to vascular dementia: [98]

- Large artery infarctions, usually cortical
- Small artery lacunar infarctions, exclusively subcortical, in the distribution of small penetrating arteries, affecting the basal ganglia, caudate, thalamus, and internal capsule as well as the cerebellum and brainstem.
- Chronic subcortical ischemia in the distribution of small arteries in the periventricular white matter and leading to selective loss of tissue elements in order of their selective vulnerability - neuron, oligodendrocyte, myelinated axon, astrocyte,& endothelial cell.

The risk factors for vascular dementia are mentioned in table D

| Table D. Risk Factors For Vascular Dementia | |
|---|---|
| **Non-reversible risk factors**<br><br>• Increasing age*<br>• Genetic predisposition (eg. CADASIL)<br>• Geographic origin (eg. African-American, Asian)<br>• Prior strokes (particularly if large, multiple, or in vulnerable locations)<br>• Low education level<br><br>***Only well established risk factor** | **Reversible risk factors**<br><br>• Hypertension<br>• Coronary artery disease<br>• Atrial fibrillation<br>• Diabetes mellitus<br>• Hyperlipidemia<br>• Hyperglycemia<br>• Smoking |

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## * VASCULAR Vs ALZHEIMER'S:

| Table E . Ischemic score (modified Hatchinski) | |
|---|---|
| Abrupt onset | 2 |
| Stepwise deterioration | 1 |
| Fluctuating course | 2 |
| Nocturnal confusion | 1 |
| Relative preservation of personality | 1 |
| Depression | 1 |
| Somatic complaints | 1 |
| Emotional incontinence | 1 |
| History of hypertension | 2 |
| History of strokes | 1 |
| Associated atherosclerosis | 2 |
| Focal neurological symptoms | 2 |
| **Maximal score =18** | |
| **Vascular range** | **7-18** |
| **Mixed range** | **5-6** |
| **Degenerative range** | **0-4** |

Various factors on the history and physical examination of patients with suspected vascular disease resulting in dementia appear to be characteristic enough that an "ischemic score" has been devised to help differentiate these patients from individuals with Alzheimer's disease. The original score assesses for the presence of 13 clinical features and attributes a score out of 18 (Table E): if the score is >7, it suggests a diagnosis of multi-infarct dementia (MID) and if <4, it suggests AD. This score has since been validated and a recent meta-analysis of pathologically confirmed MID and AD cases has been performed [99]. The authors of this meta-analysis found that the original cutoff scores allowed for correct identification of MID and AD cases in 84% and 76% of cases, respectively.

## {C}FRONTOTEMPORAL DEMENTIA :

(FTD) is a heterogeneous entity that is characterized by focal atrophy of the frontal and temporal lobes in the absence of Alzheimer.[100] Pick's disease was the first recognized subtype of FTD and is characterized pathologically by the presence of Pick bodies (silver staining intracytoplasmic inclusions) in the neocortex and hippocampus.

## {D}PARKINSON'S WITH DEMENTIA:

These include primary Parkinson's disease and Alzheimer's disease with parkinsonism. Dementia with Lewy bodies (DLB) is a fairly common cause of dementia and may present with prominent parkinsonism. Less common conditions in this category include the 'Parkinson plus' syndromes, such as multiple systems atrophy (MSA), corticobasal ganglionic degeneration (CBD), and progressive supranuclear palsy (PSP).

# PATIENTS AND METHODOLOGY

**STUDY SETTING:**

The study was conducted in **Christian Medical College Hospital, Vellore,** a 2400 bedded academic medical center in south India.

Eligible subjects were recruited from the departments of medicine, geriatrics and neurology. Currently, the department of medicine has daily out patient days (OPD), geriatrics has once a week and neurology has twice a week OPD which sees around 300, 25, 150 patients per OP day, respectively.

**STUDY DESIGN:**

A **prospective** cohort study involving 200 elderly patients with dementia.

The study design and methods were approved by the Research Committee (Institutional Review Board) of Christian Medical College, Vellore.

**SUBJECTS:**

Subjects were elderly patients above 60 years of age who were recruited from the 3 departments as mentioned earlier. The patients were residents of Tamil Nadu, Andra Pradesh, West Bengal, Jharkand and North Eastern states,in keeping with the general OPD statistics.

*** INCLUSION CRITERIA:**

- Elderly patients more than 60 years of age, who were literate and had
- Dementia as per DSM-IV criteria and MMSE (English & Tamil versions)<24.

*** EXCLUSION CRITERIA:**

- Delirium presentation
- Recent vitamin B12 injections or chronic vitamin users
- Recent history of blood transfusions
- Acute alcohol intoxication/ withdrawal
- Chronic bed bound, malnourished multi-infarct dementias

**SUBJECT ENROLLMENT:**

Ours was a prospective cohort study done between June 2006 and April 2007. All patients who presented to OPD with complaints of dementia (satisfying the inclusion criteria) were included in the study and evaluated further with detailed history, examination and MMSE. (as shown in proforma- see appendix).

**METHODOLOGY:**

The patients were asked in detail about the duration of dementia, presence of paraesthesia, anorexia, skin darkening, ataxia and visual and psychiatric problems in the past. The risk factor profile in terms of diabetes, hypertension, IHD, dyslipidemia, diet (vegetarianism) and the mean duration in months were recorded. Any significant drug history and duration of smoking in pack years were also recorded. The patients also underwent a detailed general and neurological examination. The specific type of dementia was diagnosed based on clinical criteria and laboratory data.

Subsequently, the patients were given investigations which included complete hemogram, peripheral blood smear, MCV, TSH, HIV ELISA, VDRL, B12 and folate levels, LDH and neuroimaging when indicated. B12 & folate levels were done by biochemistry lab twice a month.(colorimetric assay).

By definition, severe B12 deficiency was diagnosed when the B12 levels were less than 150pmol/L based on our lab's colorimetric assay. A level of 150-200 would indicate mild deficiency and above 200 was considered normal. In our analysis, we have **included only severe B12 deficiency (<150pmol/L).**

After a diagnosis of B12 deficiency was made, the patients were either offered admission here or in a local hospital of the patient's convenience for treatment with B12 injection. The standard B12 schedule was followed, starting with daily intramuscular injection of B12 1000mcg for a week followed by once a week for 1 month and then to continue once a month. The patients were asked to come back for follow up after 6-8 wks of treatment for a repeat MMSE.

## DATA INTEGRATION & ANALYSIS

1) Analysis of the prevalence of various dementias in elderly population presenting to our hospital.
2) Estimation of the prevalence of reversible causes of dementia with special reference to B12 deficiency.
3) Severe B12 deficiency would be further classified as isolated B12 deficiency or associated with other irreversible causes like Alzheimer's or multiinfarct state.
4) The profile of B12 deficient patients would be studied with respect to their, clinical presentation, lab parameters and dietary habits.
5) Mean MMSE analysis including sub group analysis.
6) Assessment of the improvement in MMSE after treatment with B12 injections after a 4-6 wks period.
7) Analysis of risk factors for vascular dementia.

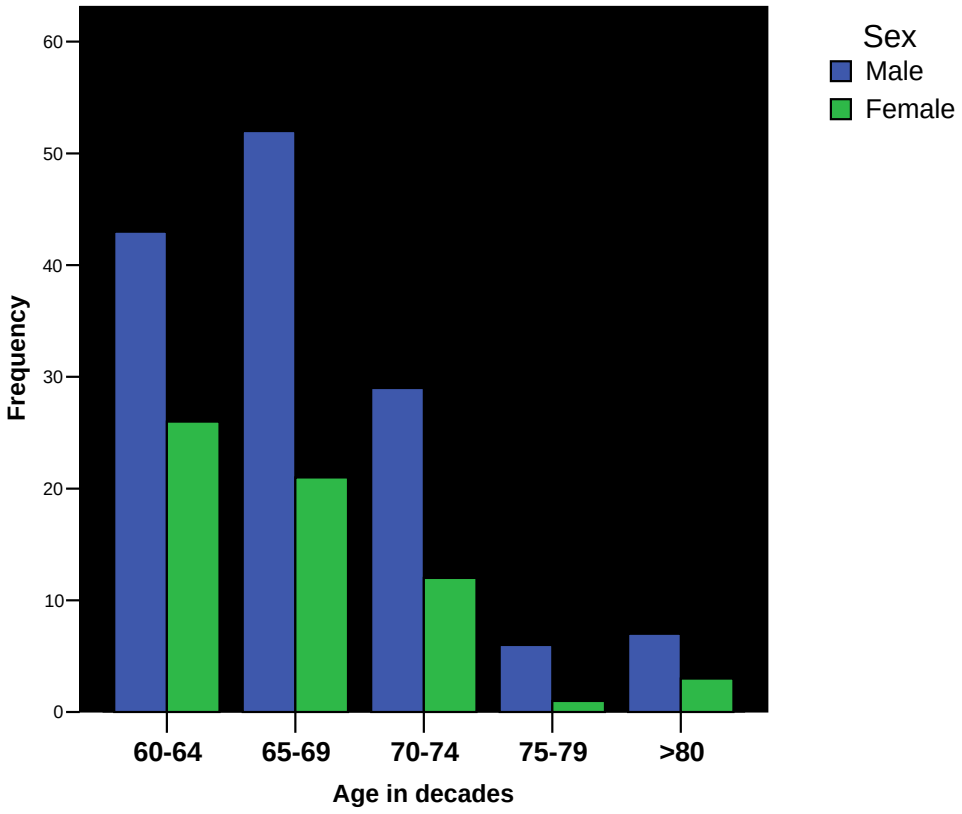
## STATISTICAL ANALYSIS:

Data entry was done using the Statistical Package for the Social Sciences (**SPSS)** software package (version **15)**. Descriptive statistics were calculated using SPSS software. Chi-square test was used for comparison of categorical variables. Odds ratio (OR) and confidence intervals (CI) were calculated and a 'p' value less than 0.05 was considered statistically significant. All reported p values are two-sided.

Table 1. Age distribution of the study population**: p =0.670**

| Age | Frequency (Percent) | ALZHEIMER'S | MULTI INFARCT | B12 DEF | MIXED |
|---|---|---|---|---|---|
| 60-69 | 142(71.0) | 30 | 51 | 15 | 11 |
| 70-79 | 48(24.0) | 8 | 23 | 5 | 4 |
| >80 | 10(5.0) | 2 | 2 | 1 | 2 |
| Total | 200(100.0) | 40 | 76 | 21 | 17 |

Figure 1. Sex distribution of the study population



# R E S U L T S

DEMOGRAPHIC DATA:

During the study period, a total of 200 patients were recruited into the study. Of these , **137(68.5%) were males**. The age and sex distribution of the study population is shown in Table 1, and represented in Figure 1.

All patients were more than 60 years of age, with maximum being in the 60-70 year age category (70%). Only 8 percent were older than 75 years.

The differences between the age groups were not significant (P-0.67 ), since most of our patients were in 60-69 age group across all causes of dementia. Thus no increasing trend was noticeable between the various groups.

Figure 2. Department wise distribution:

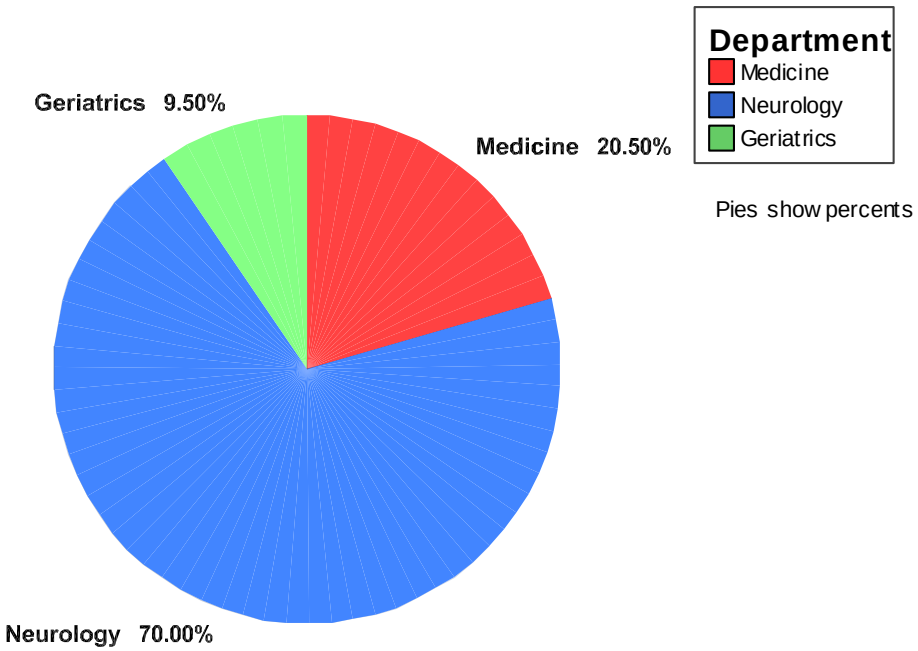
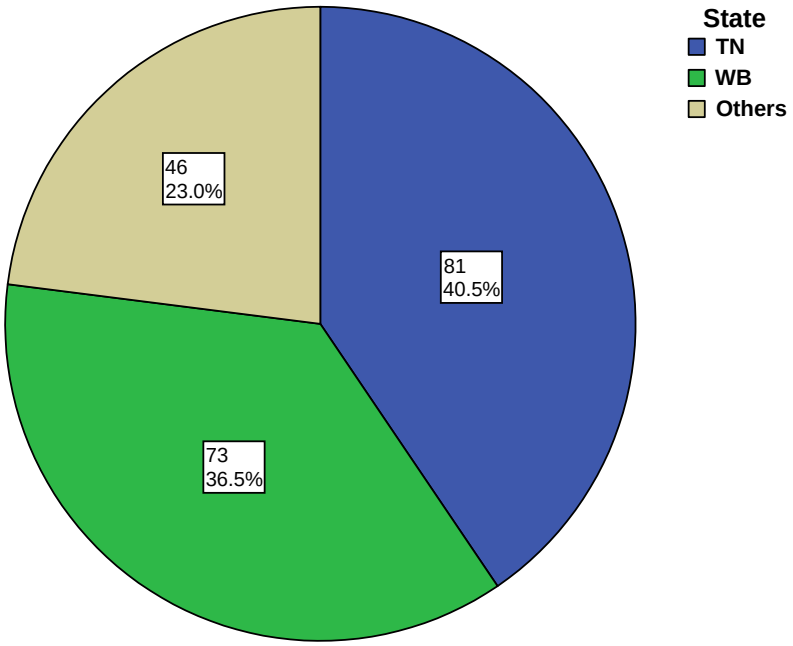



Figure 3. State wise distribution:



*** DEPARTMENT WISE DISTRIBUTION:**

As seen in figure 2, most patients were drawn from Neurology department followed by general medicine and geriatrics. The high neurology load probably was due to referral bias and patient preferences.

*** STATEWISE DISTRIBUTION:**

The state wise break up of the study population is shown in figure 3.

Most patients were local- from Vellore and surroundimg areas. But almost an equal representation was from W.Bengal and others together formed the third group.

The other states included Andra Pradesh, Jharkand, Bihar, Kerala, Assam and Karnataka.

This pattern was in keeping with the general OPD state-wise distribution.

Table 2 : Duration of dementia:

| Duration of dementia (in months) | | All patients | Alzheimer's | Multiinfarct disease | Isolated B12 deficiency | Mixed B12 deficiency |
|---|---|---|---|---|---|---|
| Median | | 36 | 54 | 42 | 10 | 60 |
| Mode | | 36 | 36 | 36 | 8 | 60 |
| Mean(±) S.D. | | 41.2±17.6 | 53.60±18.06 | 40.87±9.93 | 10±4.93 | 58.94±15.33 |
| Minimum | | 12 | 24 | 24 | 3 | 36 |
| Maximum | | 90 | 90 | 66 | 18 | 84 |
| Percentiles | | | | | | |
| | 25 | 30 | 36 | 36 | 6 | 48 |
| | 50 | 36 | 54 | 42 | 10 | 60 |
| | 75 | 48 | 70.5 | 48 | 14 | 72 |

PATIENT CLINICAL PROFILE:

*** DEMENTIA DURATION:**

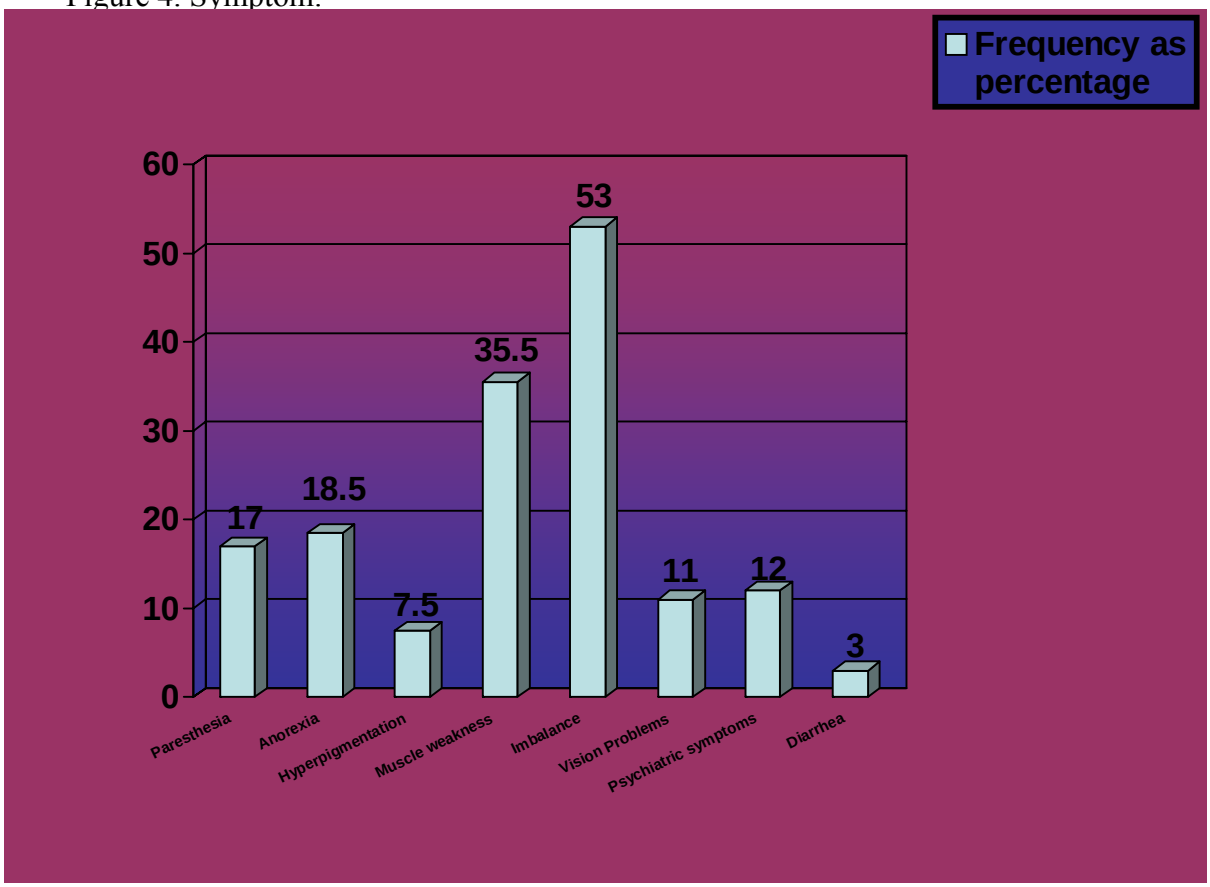
The average duration of dementia across all categories was **41.2** months. By individualizing the dementia duration with the final diagnosis, it was found that the average duration for **Alzheimer's was the longest** (53.60 months) followed by multinfarct state (40.87 months) followed by B12 deficiency (10 months).

The difference in means among the all 4 groups groups was statistically significant (p=<0.001 by ANOVA)

Table 3. Frequency of clinical features (symptoms):

| Complaint | Total | ALZHEIMER'S | MULTI INFARCT | B12 DEF | MIXED | p |
|---|---|---|---|---|---|---|
| Paresthesia | 17% | 1 | 4 | 15 | 10 | **<0.001** |
| Anorexia | 18.5% | 2 | 2 | 20 | 9 | **<0.001** |
| Hyperpigmentation | 7.5% | 0 | 3 | 9 | 3 | **<0.001** |
| Muscle weakness | 35.5% | 2 | 52 | 1 | 8 | **<0.001** |
| Imbalance | 53% | 3 | 55 | 9 | 13 | **<0.001** |
| Vision problems | 11% | 3 | 2 | 7 | 1 | **<0.001** |
| Psychiatric symptoms | 12% | 4 | 2 | 2 | 3 | 0.120 |
| Diarrhea | 3% | 0 | 0 | 4 | 1 | **<0.001** |

Figure 4. Symptom:



*** SYMPTOMS OTHER THAN DEMENTIA:**

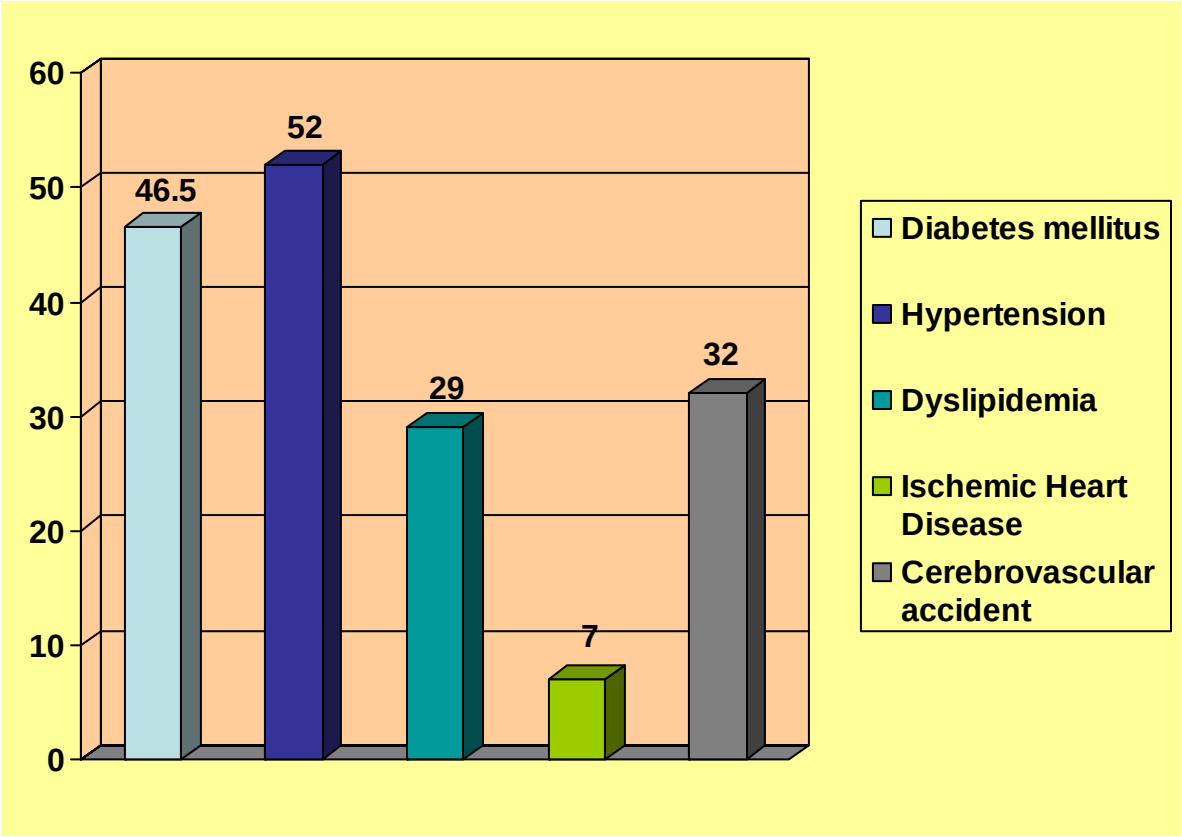
The commonest next symptom was imbalance which was seen in more than half the number of patients followed by muscle weakness which was mostly due to prior infarct, presenting as hemiparesis or hemiplegia. An equal number reported parasthesias and anorexia. Very few had reported psychiatric symptom or visual problems.

As seen from table 3, the symptoms of parasthesia, anorexia, hyperpigmentation, vision problems and diarrhea were significantly more common in B12 deficiency group whereas difficulty in walking and muscle weakness was significantly common more in the vascular dementia group.

Table 4. Comorbidity profile:

| Comorbidity | Frequency N (%) | Mean Duration in months | ALZHEIMER'S | VASCULAR | B12 DEF | MIXED | P value |
|---|---|---|---|---|---|---|---|
| DM | 93 (46.5) | 67.59 | 8 | 52 | 7 | 11 | **<0.001** |
| HTN | 104 (52) | 56.35 | 13 | 63 | 5 | 11 | **<0.001** |
| IHD | 14 (7) | 40.29 | 1 | 10 | 0 | 2 | 0.10 |
| Dyslipidemia | 58 (29) | 45.79 | 3 | 42 | 3 | 4 | **<0.001** |
| CVA | 64 (32) | 33.47 | 0 | 55 | 0 | 8 | **<0.001** |

Figure 5. Comorbidity profile distribution:



*** COMORBIDITIES:**

The comorbidity profile among the 200 patients are shown in table 4 and figure 5.

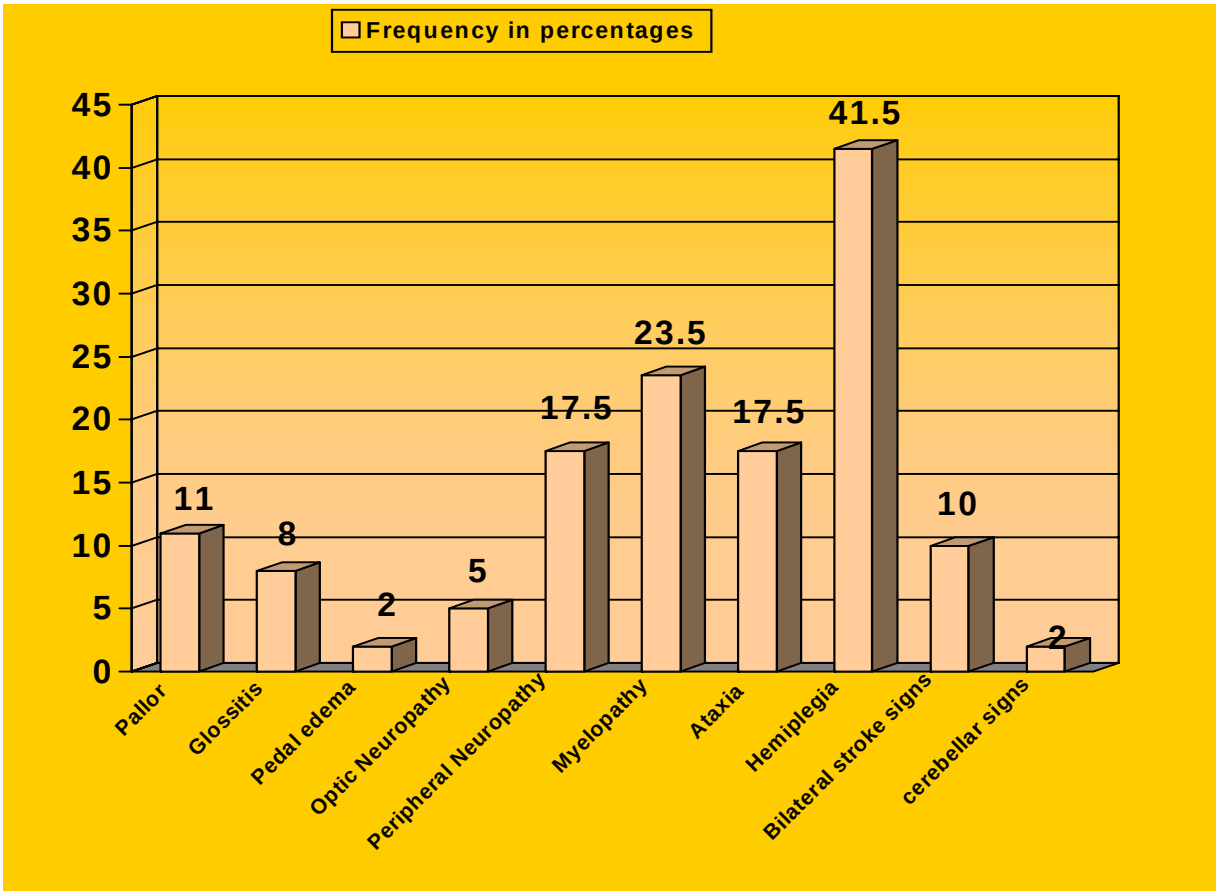
This shows that majority of the elderly population in this study were diabetic or hypertensive, and hypertensives were slightly more than the diabetics. The average duration in months were 67 and 56 months respectively.

The risk factors (except IHD) were significantly associated with vascular dementia. Only 32% had reported a previous event of stroke.

Table 5. Frequency of clinical features (signs):

| Sign | Frequency (%) | | alzheimers | vascular | B12 def | mixed | P value |
|---|---|---|---|---|---|---|---|
| Pallor | 22 | (11) | 2 | 8 | 8 | 3 | **0.003** |
| Glossitis | 16 | (8) | 0 | 1 | 12 | 2 | **<0.001** |
| Pedal Edema | 4 | (2) | 0 | 1 | 2 | 1 | 0.099 |
| Optic neuropathy | 10 | (5) | 0 | 1 | 7 | 0 | **<0.001** |
| Peripheral neuropathy | 35 | (17.5) | 1 | 0 | 18 | 13 | **<0.001** |
| Myelopathy | 16 | (8) | 0 | 0 | 11 | 5 | **<0.001** |
| Ataxia | 35 | (17.5) | 1 | 1 | 11 | 5 | **<0.001** |
| Gait not assessed | 21 | (10.5) | 40 | 62 | 21 | 15 | |
| Hemiplegia | 83 | (41.5) | 0 | 69 | 0 | 10 | **<0.001** |
| Cerebellar signs | 4 | (2) | 0 | 1 | 2 | 0 | 0.055 |
| Bilateral stroke signs | 20 | (10) | 0 | 17 | 0 | 4 | **<0.001** |

Figure 6: Clinical signs



*** CLINICAL FEATURES:**

The clinical features (signs on examination) are shown in table 5 and represented in figure 6.

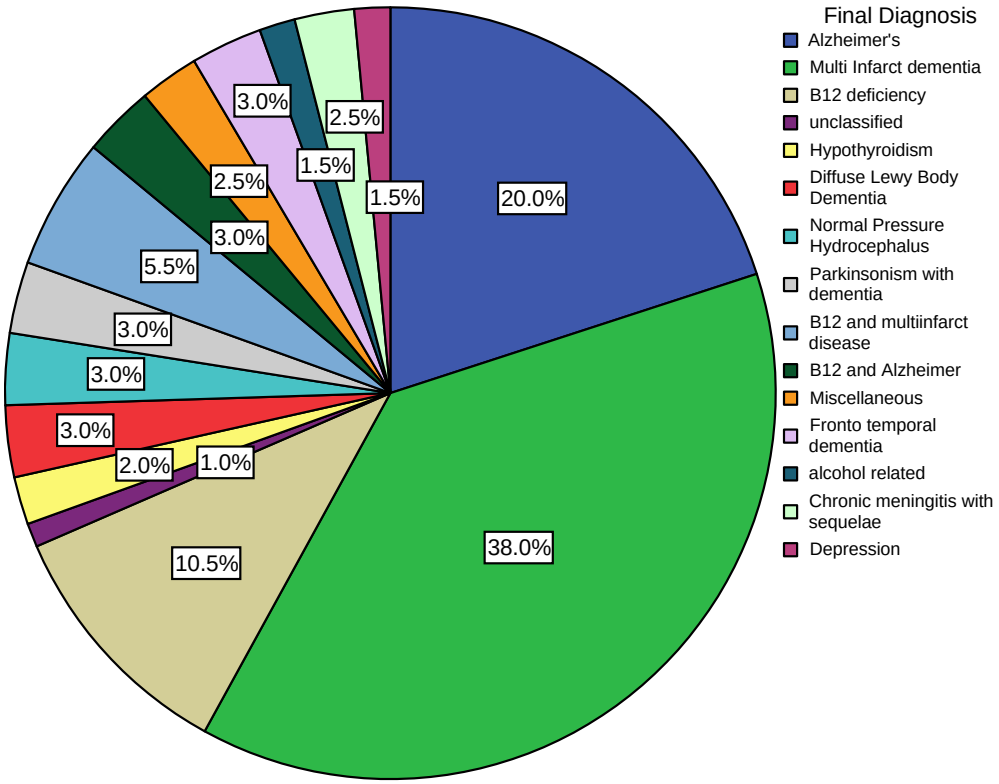
The most common finding during examination was hemiplegia. Peripheral neuropathy and myelopathy accounted for many cases as well. Many cases of multi-infarcts had bilateral pyramidal signs and the gait could not be assessed in these patients.

The features of glossitis, optic neuritis, neuropathy, ataxia and myelopathy were significantly more in B12 deficient group whereas stroke signs were much more in the vascular dementia group.

Table 6: Final Diagnosis:

| Final diagnosis | Frequency | Percent |
|---|---|---|
| Alzheimer's | 40 | 20.0 |
| Multi Infarct dementia | 76 | 38.0 |
| B12 deficiency | 21 | 10.5 |
| Unclassified | 2 | 1.0 |
| Hypothyroidism | 4 | 2.0 |
| Diffuse Lewy Body Dementia | 6 | 3.0 |
| Normal Pressure Hydrocephalus | 6 | 3.0 |
| Parkinsonism with dementia | 6 | 3.0 |
| B12 and multiinfarct disease | 11 | 5.5 |
| B12 and Alzheimer | 6 | 3.0 |
| Miscellaneous | 5 | 2.5 |
| Fronto temporal dementia | 6 | 3.0 |
| Alcohol related | 3 | 1.5 |
| Chronic meningitis with sequelae | 5 | 2.5 |
| Depression | 3 | 1.5 |
| Total | 200 | 100.0 |

Figure 7. Final Diagnosis



## FINAL DIAGNOSIS:

The final diagnosis, with respect to dementia etiology, is shown in table 6 and represented in figure 7.

The commonest cause of dementia in our study was the 2 irreversible causes (Alzheimer's and multi-infarct) accounting for more than half the study population.

Multi-infarct dementia was the commonest cause of dementia in our study followed by Alzheimer's. The third most common cause was isolated vitamin B12 deficiency which was the commonest cause among the reversible dementias.

The next most common cause was B12 deficiency in the background of Alzheimer's or multi-infarct state. This was a mixed etiology, that is, these patients had both reversible and irreversible factors.

The minor causes were NPH, Parkinsons, hypothyroidism, DLBD, FTD etc..

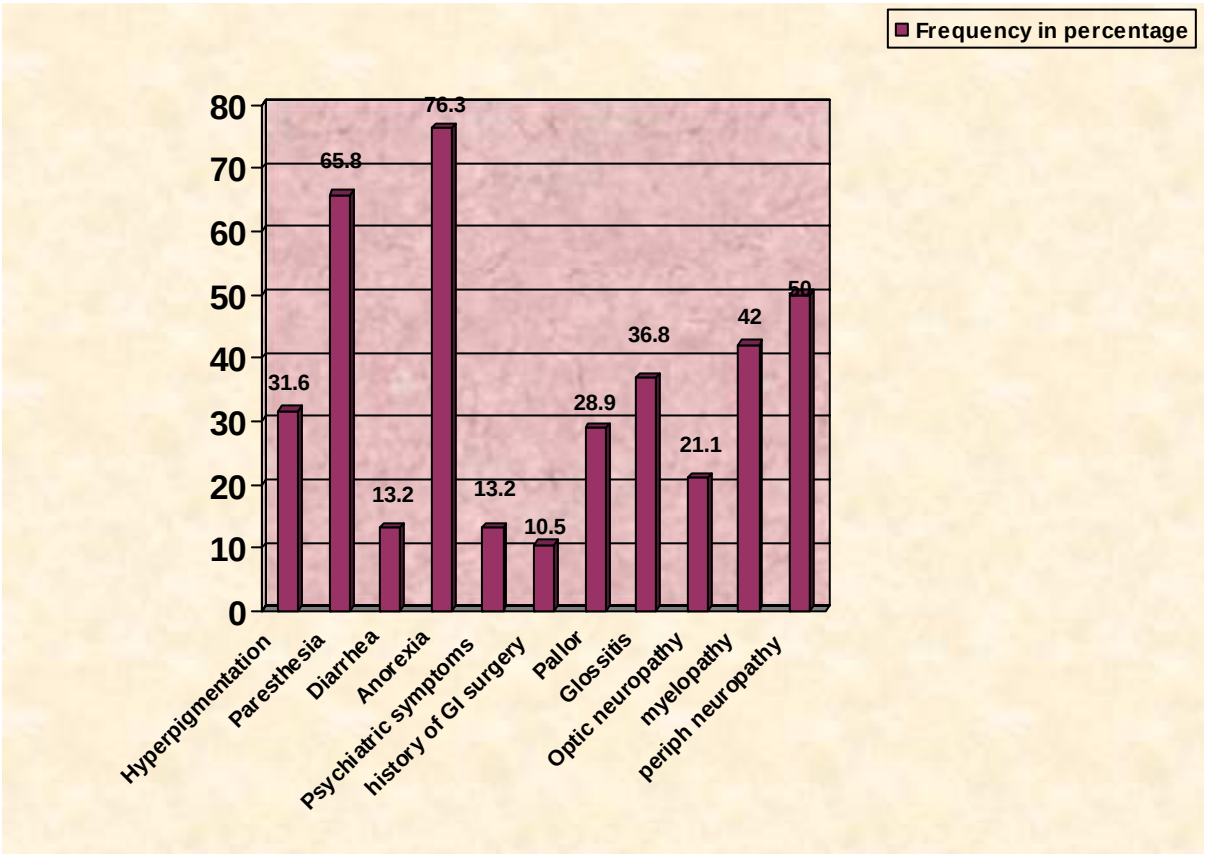
The miscellaneous causes included 1 case of AIDS dementia complex, 2 of neurosyphilis and 2 CNS tumour related.

There were 2 patients who had clinical features of Alzheimer's and also had multiple vascular risk factors but a neuroimaging was not available. These patients probably had mixed Alzheimer's and vascular dementia and were hence classified as unclassifiable.

Table 7. Clinical profile of all B12 deficient patients:

| Sign/symptom | N (%) |
|---|---|
| Hyperpigmentation | 12 (31.6) |
| Paresthesia | 25 (65.8) |
| Diarrhea | 5 (13.2) |
| Anorexia | 29 (76.3) |
| Psychiatric symptoms | 5 (13.2) |
| History of gastrointestinal surgery | 4 (10.5) |
| Pallor | 11 (28.9) |
| Glossitis | 14 (36.8) |
| Optic neuropathy | 8 (21.1) |
| Myelopathy | 16 (42) |
| Peripheral Neuropathy | 19 (50) |

Figure 8. Clinical profile distribution graph for B12 deficient patients:



## CORRELATES OF B12 DEIFICIENCY: (total-38 patients)

*** CLINICAL PROFILE OF B12 DEFICIENT PATIENTS:**

The clinical features of B12 deficient patients are shown in table 7 and represented in figure 8.

History of paraesthesia and anorexia were the most frequent symptom in all B12 deficient dementia patients. The next commonest symptom was skin hyperpigmentation and few patients also had psychiatric manifestations.

4 patients gave prior history of GI surgery which probably was the cause of B12 deficiency in these patients (small bowel surgeries, thus affecting B12 absorption)
On examination, 11 had pallor and 14 had glossitis. 8 patients had optic neuropathy due to B12 deficiency of which 6 were documented by the ophthalmologists.

Neurological involvement was quite common in our study. 8 patients satisfied the criteria for subacute combined degeneration. 19 (50%) patients had features of peripheral neuropathy which was predominantly more sensory. 16 (42%) patients had myelopathy. Totally 23 (68%) patients had other neurological findings other than the syndrome of dementia. Neuropsychiatric symptoms were seen in 5 patients which included depression, hypomania, paranoid psychosis with auditory or visual hallucinations.

Table 8. Correlation between type of diet and B12 deficiency:

| B12 deficiency and diet correlation (p<0.001) | | Diet | | Total |
|---|---|---|---|---|
| | | Vegetarian | Non Vegetarian | |
| B12 levels | normal | 21 | 141 | 162 |
| | deficient | 22 | 16 | 38 |
| Total | | 43 | 157 | 200 |

Table 9. Correlation between peripheral blood picture and B12 deficiency: (p<0.001)

| | | Peripheral blood smear | | | | Total |
|---|---|---|---|---|---|---|
| | | Normal | Hypochromic Microcytic | Megaloblastic | Dimorphic | |
| B12 | normal | 144 | 16 | 2 | 0 | 162 |
| | deficient | 7 | 1 | 27 | 3 | 38 |
| Total | | 153 | 17 | 29 | 1 | 200 |

Table 10. 2*2 table of Perpheral blood smear with B12 (p<0.001)

| | | B12 deficient | Normal B12 | Total |
|---|---|---|---|---|
| PBS | megaloblastic | 27 | 2 | 29 |
| | Normal/hypo | 11 | 160 | 171 |
| Total | | 38 | 162 | 200 |

*** Association of diet with B12 deficiency:** $p < 0.001$

In our study, as seen in table 8, there was a significant correlation between vegetarian diet and B12 deficiency when compared to the rest of the study patients. ($p<0.001$). 22 out of 38, B12 deficient patients were vegetarians. This was in keeping with the known fact that a vegetarian diet predisposes a person to developing B12 deficiency. The odds ratio for vegetarians to develop B12 deficiency was significantly increased as compared to non-vegetarians **8.41** (95% confidence interval between 3.81 to 18.34).

*** Peripheral blood smear and B12 deficiency**( $p < 0.001$)

As seen in table 9, 27 out of 38 patients had a megaloblastic blood picture , with, hypersegmented neutrophils, basophilic stippling, ovalocytes and macroovalocytes. The association between B12 deficiency and megaloblastic blood picture was significant ($p<0.001$). 7 patients had a normal blood picture though their B12 levels were very low. And 3 patients had a dimorphic blood picture with both megaloblastic and microcytic changes. Only 1 patient had hypochromic and microcytic blood picture despite low B12 levels.

As derived from table 10, the sensitivity and specificity of peripheral blood smear in diagnosis of B12 deficiency is **71% and 98.7%** respectively. The positive and negative predictive value for the same is 93.1% and 93.5%.

Table 11. Correlation of MCV with B12 deficiency: (p<0.001)

| | | N | Mean | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|
| MCV | With B12 deficiency | 38 | 99.487 | 12.4813 | 2.0247 |
| | Without B12 deficiency | 162 | 84.722 | 6.7838 | .5330 |

Table 12. 2*2 table for MCV and B12 def: (p=0.01)

| | | B12 deficient | Normal B12 | Total |
|---|---|---|---|---|
| MCV | high | 25 | 5 | 30 |
| | Low/normal | 13 | 157 | 180 |
| Total | | 38 | 162 | 200 |

Table 13. Anemia in the study population: (P=0.011)

| | | Normal | B12 deficient | Total |
|---|---|---|---|---|
| Hb | Anemia | 39 | 17 | 56 |
| | Normal | 123 | 21 | 144 |
| Total | | 162 | 38 | 200 |

*** Association between MCV and B12 deficiency** ($p < 0.001$)

As seen in table 11, there was a significant correlation between high MCV and B12 deficiency. The average MCV was 99.4 in B12 deficient patients and 84.7 in others. It is interesting to note that 8 patients had a normal MCV and 5 patients had low MCV with low B12 levels.

As derived from table 12, sensitivity and specificity of MCV in B12 deficiency is **62.5% and 96.9%**, respectively. The positive and negative predictive values for the same are 83.3% and 92.3% respectively.

*** Proportion of anemia in study population**: ($p=0.01$)

Out of the 200 recruited, 56 had anemia. As seen in table 13, there was a significant correlation of anemia with B12 deficiency, in that, there was a higher proportion of anaemic patients in the B12 deficient group compared to the others.

Table 14. Correlation between platelet count / total count and B12 deficiency: (p=0.01)

| | | Platelet count | | Total |
|---|---|---|---|---|
| | | low | normal | |
| B12all | No deficiency | 44 | 118 | 162 |
| | deficiency | 24 | 14 | 38 |
| Total | | 68 | 132 | 200 |
| | | Total count | | Total |
| | | low | normal | |
| B12all | No deficiency | 1 | 161 | 162 |
| | deficiency | 5 | 33 | 38 |
| Total | | 6 | 194 | 200 |

Table 15. Correlation between LDH and B12 deficiency: (p<0.001)

| | | B12 deficient | Normal B12 | Total |
|---|---|---|---|---|
| LDH | high | 26 | 3 | 29 |
| | raised | 8 | 117 | 125 |
| Total | | 34 | 120 | 154 |

*** Association of thrombocytopenia( p = 0.01) and leucopenia( p = 0.01) with B12 deficiency:**

There was significant association between thrombocytopenia and leucopenia with B12 deficiency as compared to others.

Hence from past 2 tables, it is evident that pancytopenia is more common in B12 deficiency state.

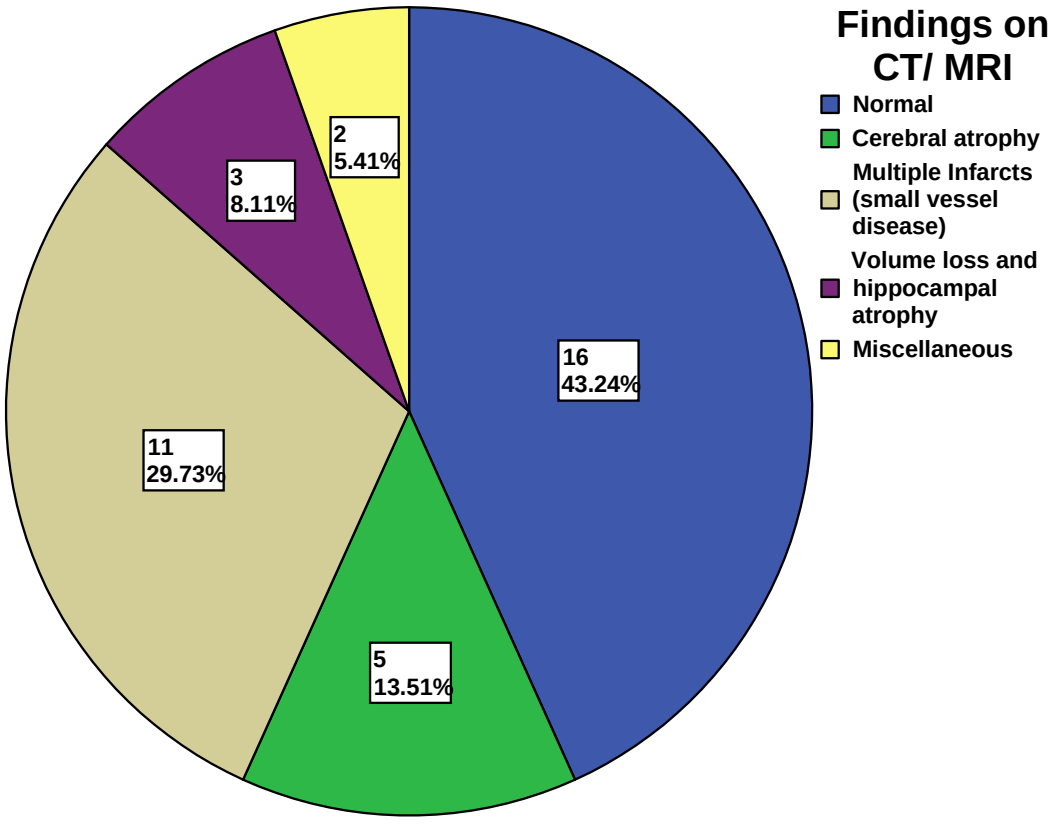
*** Correlation of LDH with B12 deficiency:** ($p<0.001$)

As seen from table 15, the sensitivity and specificity of LDH in B12 deficiency is **76.4% and 97.5%** respectively. The positive and negative predictive value for the same is 89.6% and 93.6% respectively.

Table 16. CT/MRI findings in B12 deficient patient:

| | | Frequency | Percent | Valid Percent |
|---|---|---|---|---|
| | Normal | 16 | 42.1 | 43.2 |
| | Cerebral atrophy | 5 | 13.2 | 13.5 |
| | Multiple Infarcts(small vessel disease) | 11 | 28.9 | 29.7 |
| | Volume loss and hippocampal atrophy | 3 | 7.9 | 8.1 |
| | Miscellaneous | 2 | 5.3 | 5.4 |
| | Total | 37 | 97.4 | 100.0 |
| Total | | 38 | 100.0 | |

Figure 9. Pie diagram for neuroimaging in B12 deficiency:



*** Imaging studies in patients with B12 deficiency:**

For patients with isolated B12 deficiency patients, neuroimaging was normal except the 2 patients with SCD (labelled miscellaneous) who had hyperintensities of posterior column on MRI. 28.9% and 7.9% had features of multi-infarct and alzheimer's respectively on neuroimaging.

The features on MRI/CT to suggest a multi-infarct state was either multiple small lacular infarcts or periventricular hyperintesities suggestive of small vessel disease.

The neuroimaging features of Alzheimer's were either a normal imaging (since it has low sensitivity and high specificity) or features to suggest volume loss ( actual volume was not measured) and hippocampal atrophy.

Figure 10. Mean MMSE distribution:

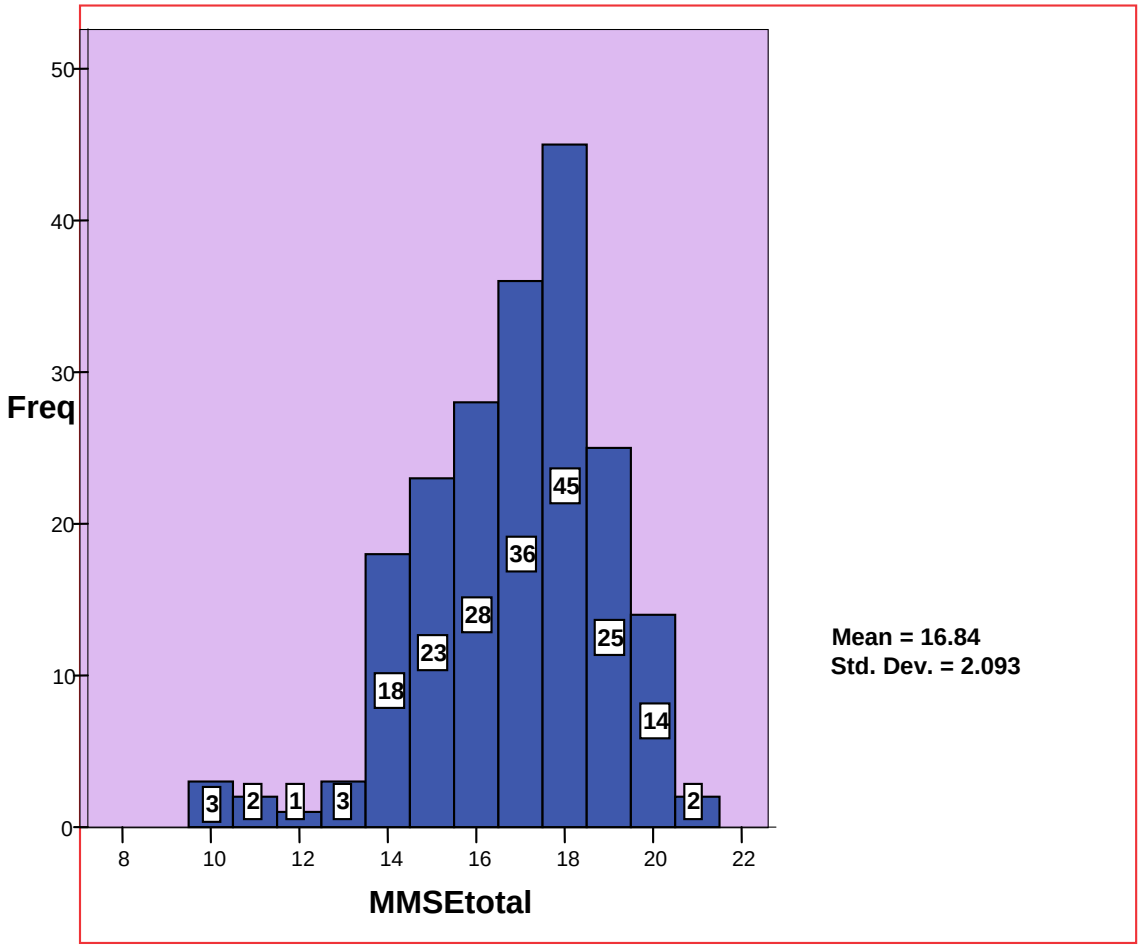



Table 17. MMSE score differences

| MMSE scores | All patients | Alzheimer's | Multiinfarct disease | Isolated B12 deficiency | Mixed B12 deficiency |
|---|---|---|---|---|---|
| Mean | 16.08 | 15.95 | 16.68 | 13.62 | 13.00 |
| Median | 16.00 | 16.00 | 17.00 | 14.00 | 13.00 |
| Mode | 16 | 16 | 18 | 14(a) | 15 |
| S.D | 2.109 | 1.584 | 1.368 | 1.910 | 1.969 |
| Minimum | 10 | 13 | 14 | 10 | 10 |
| Maximum | 21 | 19 | 19 | 16 | 16 |

## MMSE ANALYSIS:

*** Total MMSE:**

The total MMSE score distribution is depicted in figure 10. The average MMSE score was 16 and had a bell shaped distribution.

*** Difference in MMSE scores:**

The MMSE scores were significantly lower in patients with B12 deficiency as compared to those with Alzheimer's($p = 0.008$), and to those with multi infarct state($p = 0.003$).

There was also a significant difference between patients with Alzhiemer's disease and multiinfarct state($p=0.01$)

Table 18: Comparison of MMSE domains between Alzheimer's & B12 deficiency:

| MMSE DOMAINS | Alzheimer's (n=40) | B12 deficiency (n=21) | P value |
|---|---|---|---|
| ORIENTATION (10) | 5.25 | 5.19 | 0.816 |
| REGISTRATION (3) | 1.78 | 1.43 | **0.017** |
| CALCULATION (5) | 2.80 | 1.86 | **<0.001** |
| RECALL (3) | 1.68 | 1.43 | 0.065 |
| LANGUAGE & DRAWING(9) | 4.40 | 3.71 | **0.037** |

Table 19: Comparison of MMSE domains between Multi-infarct & B12 deficiency:

| MMSE DOMAINS | Multiinfarct state (n=76) | B12 deficiency (n=21) | P value |
|---|---|---|---|
| ORIENTATION (10) | 6.17 | 5.19 | **<0.001** |
| REGISTRATION (3) | 1.80 | 1.43 | **<0.001** |
| CALCULATION (5) | 2.76 | 1.86 | **<0.001** |
| RECALL (3) | 1.74 | 1.43 | **0.007** |
| LANGUAGE & DRAWING (9) | 4.17 | 3.71 | 0.081 |

Table 20: Comparison of MMSE domains between Alzheimer's & multi-infarct:

| MMSE DOMAINS | Alzheimer's (n=40) | Multi-infarct state (n=76) | P value |
|---|---|---|---|
| ORIENTATION (10) | 5.25 | 6.17 | **<0.001** |
| REGISTRATION (3) | 1.78 | 1.80 | 0.753 |
| CALCULATION (5) | 2.80 | 2.76 | 0.694 |
| RECALL (3) | 1.68 | 1.74 | 0.487 |
| LANGUAGE & DRAWING (9) | 4.40 | 4.17 | 0.223 |

* MMSE SUBGROUP ANALYSIS:

As derived from table 18, in the analysis between Alzheimer's and B12 deficiency, the difference in registration and calculation was significant. Hence,

As derived from table 19, in the analysis between vascular and B12 deficiency, the differences in all variables except language and figure drawing were significant.

From the above 2 tables, it can be derived that B12 deficiency affects preferentially more registration and calculation and Alzheimer's affects more of orientation and recall.

Table 21. MMSE scores before and after (6wks) of B12 correction:

| P =<0.001 | | MMSE before Rx | MMSE after Rx |
|---|---|---|---|
| N | Valid | 38 | 29 |
| | Missing | 0 | 9 |
| Mean | | 13.34 | 21.10 |
| Median | | 14.00 | 20.00 |
| Mode | | 15 | 18(a) |
| Std. Deviation | | 1.935 | 4.670 |
| Minimum | | 10 | 14 |
| Maximum | | 16 | 29 |

Table 22. Mean improvement in MMSE scores in the two B12 categories:

| p = 0.001 for both | | N | Mean | Std. Deviation |
|---|---|---|---|---|
| Improvement in MMSE scores | Isolated B12 deficiency | 16 | 10.6250 | 4.91087 |
| | B12 with multi infarct/ Alzhiemer's | 13 | 3.9231 | 2.28989 |

*** MMSE AFTER TREATMENT IN B12 DEFICIENT PATIENTS:**

Shown in table 21 are MMSE scores measured after 6-8wks of treatment for B12 deficiency. Most patients were admitted in our hospital for initiating treatment and the rest were advised treatment under a local physician (mostly local patients) and all were asked to review after 6-8 wks. 9 patients with B12 deficiency were lost to follow up and the MMSE could not be measured. Most of the patients, who were lost to follow up, were from North India.

Of those who were followed up, the mean improvement in MMSE was from 13.34 to 21.10 , that is a improvement by 8 points which is a significant considering the average MMSEs of other types. The best improvement was by 13 points in 1 patient and the least was by 4 points in a patient who had concommitant multi-infarct state.

*** MMSE IMPROVEMENT IN ISOLATED B12 DEFICIENT COMPARED WITH MIXED DEMENTIA:**

This improvement in MMSE after treatment was more marked in those with isolated B12 deficiency as compared to those with B12 deficiency associated with other comorbidities like multiinfarct disease or Alzheimer's disease ($p<0.001$). In terms of absolute values, in isolated B12 deficiency there was improvement by **10** points versus **4** points for B12 deficiency associated with other co-morbidities.

*** OTHER FEATURES AFTER TREATMENT:**

1) Anorexia: This symptom had the most dramatic improvement. Most patients (90%) got back their appetite fully within 2 weeks.

2) Peripheral neuropathy: The symptom of paraesthesia had improved in 20 patients but on examination, they still had some features of neuropathy, which probably was improving and would need to be re-assessed later.

3) Ataxia: This symptom showed only mild improvement. Those patients who had ataxia still persisted to have mild gait imbalance.

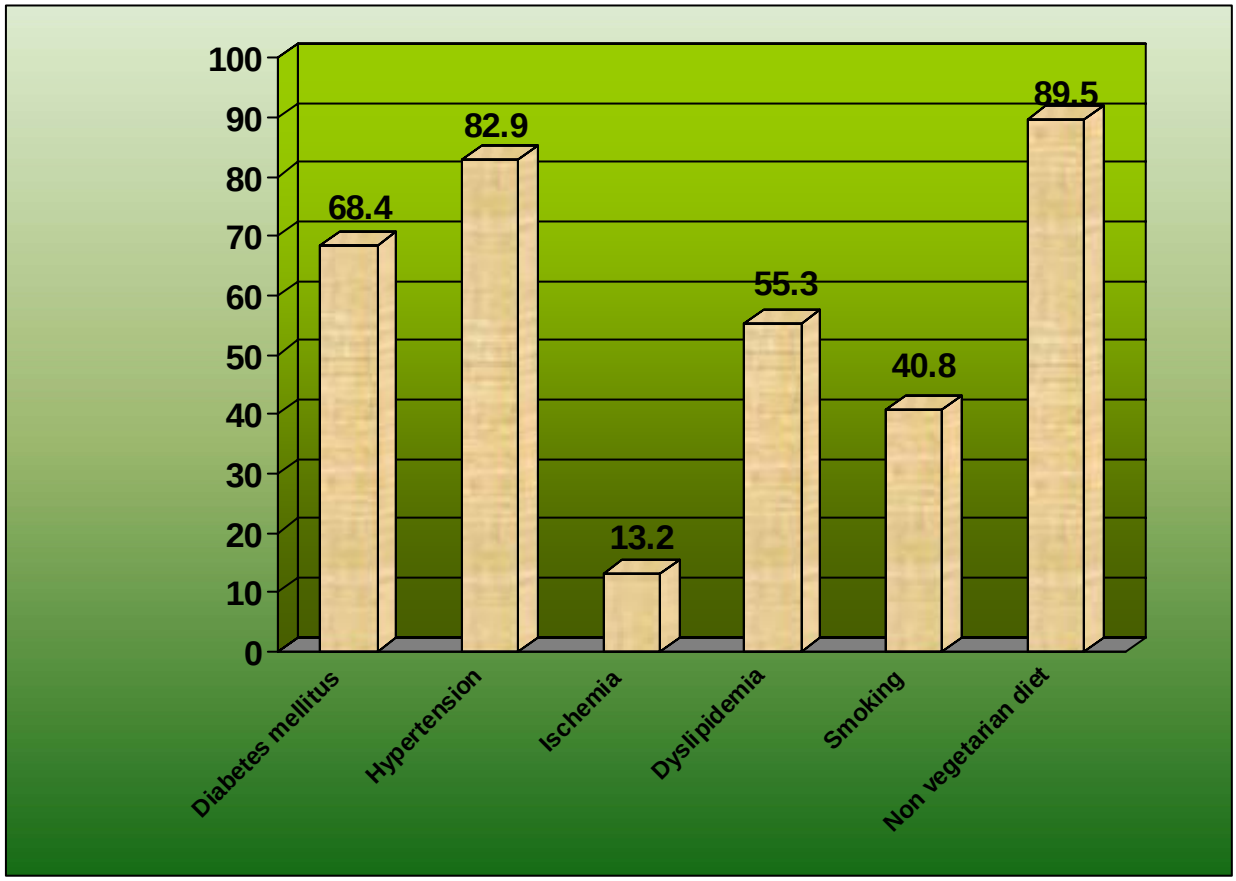
4) Myelopathy: The deep tendon reflexes normalized in 2 patients but no change in plantar response. This sign also needs periodic assessment and probably was assessed too early.

5) Optic Neuropathy: This symptom did not show any improvement

Table 23. Comorbidities in multi-infarct state:

| Comorbidities | Frequency<br>N<br>90 | <br>(%)<br>(100) |
|---|---|---|
| Diabetes mellitus | 52 | (68.4) |
| Hypertension | 63 | (82.9) |
| Ischemic heart disease | 10 | (13.2) |
| Dyslipidemia | 42 | (55.3) |
| Smoking | 31 | (40.8) |
| Diet | 68 | (89.5) |

Figure 11. Comorbidity profile graph for multi-infarct state.



## *MULTIINFARCT STATE PATIENT PROFILE:

### * COMORBIDITY PROFILE:

The comorbidity profile of multi-infarct dementia is shown in table 23 & figure 11.

The biggest risk factor for developing multi-infarct state in our study was hypertension (83%) followed by diabetes (71%). 70% had both diabetes and hypertension co-existing. The next set of risk factors were dyslipidemia and smoking. A vast majority of the patients were non vegetarians.

Among a total of 84 patients with multiinfarct features on CT/MRI, only 62 (79%) had a history of CVA. So in our study 26% of patients with multiinfarct state did not give a past history of stroke.

Table 24. Correlation between risk factors and multi-infarct state:

| Average duration of risk factor in months | | N | Mean | Std. Deviation | p |
|---|---|---|---|---|---|
| Diabetes Mellitus | In patients without multi infarct disease | 41 | 55.32 | 24.354 | **<0.001** |
| | In patients with multi infarct disease | 52 | 77.27 | 25.878 | |
| Hypertension | In patients without multi infarct disease | 41 | 46.49 | 22.008 | **0.001** |
| | In patients with multi infarct disease | 63 | 62.76 | 23.972 | |
| Ischemic Heart Disease | In patients without multi infarct disease | 4 | 48.00 | 24.000 | 0.358 |
| | In patients with multi infarct disease | 10 | 37.20 | 17.158 | |
| Dyslipidemia | In patients without multi infarct disease | 16 | 40.75 | 21.038 | 0.294 |
| | In patients with multi infarct disease | 42 | 47.71 | 22.874 | |
| Smoking (pack years) | In patients without multi infarct disease | 23 | 45.17 | 17.463 | 0.516 |
| | In patients with multi infarct disease | 31 | 48.16 | 15.952 | |

Table 25. Correlation between type of diet and multi-infarct state:

| P = 0.003 | | Multiinfarct Yes | No | Total |
|---|---|---|---|---|
| Diet | Vegetarian | 35 | 8 | 43 |
| | Non Vegetarian | 89 | 68 | 157 |
| Total | | 107 | 124 | 76 |

Table 26. Correlation between alcohol and multi-infarct state

| P = 0.003 | | Multiple infarcts on imaging Yes | No | Total |
|---|---|---|---|---|
| Alcohol Intake | Absent | 89 | 54 | 143 |
| | Present | 18 | 30 | 48 |
| Total | | 107 | 84 | 191 |

*** CORRELATION BETWEEN RISK FACTORS & MULTI-INFARCT:**

Among the various risk factors mentioned, diabetes and hypertension had the maximum correlation with development of a multi-infarct state and dyslipidemia also had an increased risk. Surprisingly smoking did not have a significant correlation ($p=0.85$). This was probably due to almost equal but high rates of smoking among almost all participants.

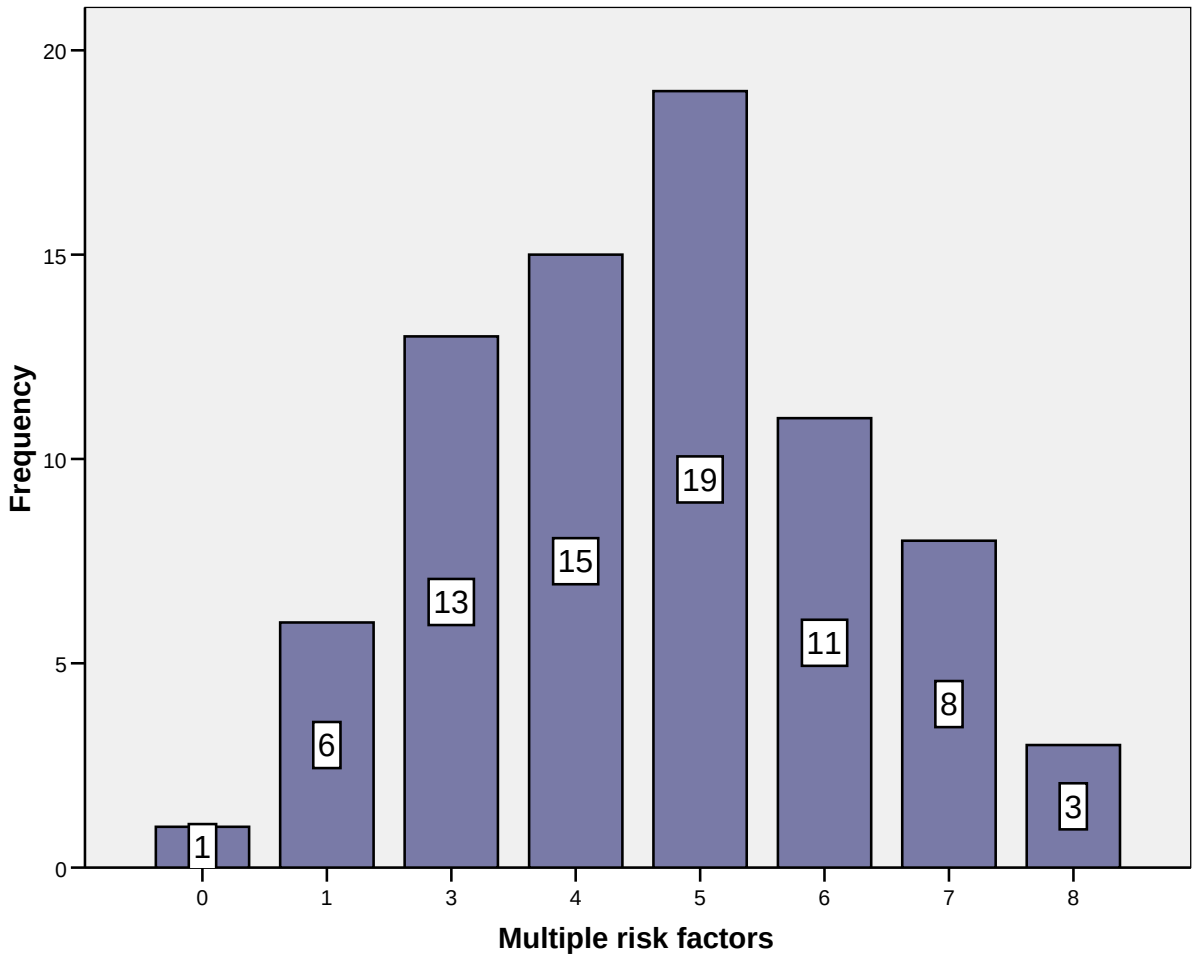
*** CORRELATION BETWEEN DIET & MULTI-INFARCT:**

Non vegetarian diet was associated with a higher risk of multi-infarct dementia as compared to the other categories of dementia.

*** CORRELATION BETWEEN ALCOHOL & MULTI-INFARCT:**

There was a significant correlation between the alcohol intake and development of multi-infarct state.

Figure 12. Risk for multi-infarct state:



*** RISK FACTORS IN MULTIINFARCTS:**

73 patients had 3 or more risk factors. And higher the risk factors, higher the chance of developing multi-infarct state. 1 patient had absolutely no risk factors and had developed multiinfarct state.

This results shows that multi-infarct state is very strongly associated with multiple risk factors.

# D I S C U S S I O N

This study was a prospective study in an Indian population recruiting 200 elderly patients (>60 years) with dementia and studying the causes for dementia and estimating the prevalence of B12 deficiency as the cause of dementia and also to assess the effects on MMSE after treatment.

*** POPULATION PROFILE:**

In this study, the population selected was above 60 years and most of them were between the 60-70 year group and were predominantly males (68.5%).
All of them had dementia as defined by DSM IV and MMSE less than 24.

The average duration of dementia was **41 +/- 17** months. There was a significant difference in the duration between the various groups of dementia. Alzheimer's dementia was the longest duration with mean of 53 months followed by multi-infarct- 40months and B12 deficiency- 10 months. This finding was in keeping with the studies done by ***Nagaraja et al*** [26] in India and ***Larson et al*** [27] in USA, where the duration of dementia was shorter in the B12 deficient group compared to degenerative dementias. The duration in the previous CMC study was 10.3 months. The implication is that reversible causes including B12 deficiency needs to be suspected in the setting of recent onset rapidly progressing dementia.

Most of the patients complained of inability in walking, muscle weakness, anorexia and parasthesias. The most commonest finding was peripheral neuropathy due to diabetes and B12 deficiency. It is interesting to note that 46% had diabetes and 52% had hypertension.

*** CAUSE OF DEMENTIA:**

In our study, irreversible dementias were the commonest cause accounting totally for about **68%** of cases and reversible dementias accounts for **25%** of cases. Nearly 7% were due to mixed causes, that is, they had both a reversible cause (B12 deficiency) and irreversible cause (either multi-infarct or Alzheimer's). Only 2 cases were unclassifiable since they may have had features of Alzheimer's and multi-infarct.

Compared to prior studies, there was a marked difference in our results. As compared to study by ***Hejl et al*** [5], the commonest causes for reversible dementia was depression and alcohol related. In the same study, the reversible causes accounted for 19% cases. In the meta-analysis [6], 13% had reversible causes and again the commonest causes were drugs, depression and metabolic causes.

Among the irreversible causes, the commonest was vascular dementia (**37.5%**) followed by Alzheimer's (**20%**) which is in keeping with the study done by ***RajKumar et al*** [16] in suburbs of Chennai ,***Varghese et al*** [17] in rural Kerala and SGPGI study. This finding in our study substantiates the fact that vascular dementia is the commonest cause of dementia in Indian population.

*** MMSE VALUES:**

The average MMSE in our study population was **16** and 90% of the patients were between 14-20. Hence most of our patients were severely demented.

The average MMSE values showed significant differences between the groups. The lowest MMSE was recorded for reversible dementia due to B12 deficiency (**13.62**) whereas the irreversible dementias had better scores (alzheimer's-**15.95** and multi-infarct

state-**16.98**). This finding was contrary to what was found by ***Nagaraja et al*** [26] and ***Larson et al***[27]**.** This probably was due to the fact that the B12 deficient patients who presented to us were in an advanced stage of the disease as evidenced by large proportion of neurological findings including myelopathy , neuropathy and optic neuropathy. The least MMSE scores, in our study, was in the mixed B12 deficient group which had associated irreversible causes.

B12 deficiency, in our study, seems to affect preferentially more registration and calculation and Alzheimer's affects more of orientation and recall. The clinical significance of this may not be relevant as the differences are in decimal points only since each domain can have maximum of 3-5 points only. Hence this may be just a trend seen in our study and would need further validation using a larger sample size.

*** B12 DEFICIENT PATIENT PROFILE:**

This group accounted for 19% of cases and was divided into 2 different causes- isolated B12 deficiency which was 10.5% and B12 deficiency associated with irreversible causes which was 8.5%.

In other international studies mentioned earlier [29,30,31], the frequency of B12 deficient dementia varied between 9-25%. In other Indian studies, the frequency was 7% and the sample size was around 100. ***Yajnik's*** study [35] found a high proportion of patients with asymptomatic B12 deficiency (upto 60% in rural population).

Many patients complained of paraesthesia (25%) and anorexia (29%) which were the main 2 symptoms in this group. 5 patients also reported psychiatric symptoms.
As mentioned earlier it is interesting to note that many patients had neurological manifestations. All had dementia and a majority had peripheral neuropathy (50%)- mainly sensory. Many also had features of myelopathy (40%) and optic atrophy (20%). 8 patients had optic neuritis and 8 patients had subacute combined degeneration, thus indicating that the B12 deficient population in our study had advanced B12 deficiency.

A vegetarian diet was significantly associated with B12 deficiency with an odds ratio of **8.4.** This finding correlates with earlier study by Yajnik on vegetarianism and B12 deficiency.[35]

*** LABORATORY FEATURES OF B12 DEFICIENCY:**

In our study the B12 assay was taken as the gold standard and a value of less than 150 pmol/L was considered to be very low.

MCV, peripheral blood smear and LDH were 3 good markers for B12 deficiency. They all had low sensitivities but had very high specificities (>95%). Hence, if present in high values, they point towards B12 deficiency. Also it is important to remember that a normal MCV, PBS and LDH does not rule out B12 deficiency. In our study, of all those with B12 deficiencies**, 13, 11 and 8 patients had normal** or lower values of MCV, PBS and LDH respectively. This was similar to the findings of the CMC [37] study in which 17% had normal MCV.

There was a significant correlation between anemia, thrombocytopenia and leucopenia in B12 deficiency suggesting that pancytopenia is also a feature.

Anemia was significantly associated with B12 deficiency in the CMC study [37] and SGPGI study [36].

Hence in our study, factors which **predicted a reversible cause** (B12 deficiency) were-

- shorter duration of dementia
- severe dementia (very low MMSE scores)
- Lower MMSE scores in attention, language and re-call
- Symptoms of parasthesia, anorexia, hyperpigmentation, visual symptoms, diarrhea
- presence of focal neurological signs – neuropathy, myelopathy, optic neuritis, psychiatric features
- vegetarian diet
- Lab features- high MCV, megaloblastic blood picture and high LDH.

*** CHANGES AFTER B12 ADMINISTRATION:**

There was follow up available only in 29 out of the 38 B12 deficient patients. There was significant improvement in MMSE by an average of 8 points overall and when this was further split up, there was an improvement by **10** in the isolated b12 deficiency group and by only **4** in the mixed group. This suggests that in the patients with mixed etiology, the irreversible causes contributed more to the dementia than b12 deficiency.

The symptoms of anorexia and peripheral neuropathy showed significant improvement in 6-8 wks after treatment and there was minimal improvement in myelopathy and ataxia as well but this probably needs a longer follow up. This result is in

keeping with previous studies in which the neurological symptoms have improved rapidly since the patients presented within 1 year of illness and presence of myelopathy probably indicated a worser prognosis since there was hardly any improvement. But these patients need longer follow up to re-assess myelopathy.

*** MULTI-INFARCT DEMENTIA:**

The biggest risk factor for developing multi-infarct state in our study was hypertension (83%) followed by diabetes (71%). 70% had both diabetes and hypertension co-existing. The next set of risk factors were dyslipidemia and smoking.

There was significant risk associated with diabetes, hypertension, dyslipidemia, non vegetarian diet and alcohol consumption.

## LIMITATIONS OF THE STUDY:

1) Bone marrow testing was not done routinely for all and this was not taken into account in the analysis of our data.

2) Neuroimaging could not be done for 6 patients due to financial problems.

3) Among those with B12 deficiency, follow up was available only in 29 on 38. That is 24% were lost to follow up.

4) The follow up period was only 6-8 weeks after treatment for B12 deficient patients. Even with this short follow up, the patients showed significant improvement in MMSE and neurological parameters. Hence a longer follow up is ideal to see if these improvements are sustained.

5) The MMA and HC levels could not measured since. But this could not have affected out study results since the indication for doing these 2 tests are when the B12 level is between 200-300pmol/L (15 patients) and all the B12 deficient patients included in our study had B12 <150pmol/L. Hence we may have underestimated the number of B12 deficiency.

# C O N C L U S I O N S

1) In our study population, vascular dementia **(38%)** was more common than Alzheimers **(20%)** probably due to the high prevalence of diabetes and hypertension.
2) The proportion of reversible dementias were much higher **(25%)** than other earlier studies and the most common among these was B12 deficiency **(19%).**
3) The average duration to presentation was much shorter in B12 deficiency (10mths).
4) MMSE was much lower in B12 deficiency **(13)** compared to irreversible causes **(16)**
5) Thus shorter duration, severe dementia, focal neurological signs and vegetarian diet was significantly associated with development of B12 deficiency.
6) In the diagnosis of B12 deficiency, MCV, peripheral blood smear and LDH had relatively **low sensitivities** (62.5%,71% &72.4% respectively) but very **high specificities** (98.7%, 96.9% &97.5% respectively).
7) B12 deficiency seems to affect more of registration and calculation whereas Alzheimer's seems to affect more of orientation and recall.
8) There was a significant and marked improvement in MMSE after treatment in pure B12 deficient patients (by **10** points) if they presented within 1 year of symptoms. There was improvement in other neurological parameters except myelopathy.
9) Multi-infarct state was significantly associated with risk factors- diabetes, hypertension, dyslipidemia, non vegetarian diet and alcohol intake.

Considering this marked improvement and a high prevalence of B12 deficiency in elderly population, we recommend that **B12 levels be done for all elderly dementia patients** as it is a potentially treatable cause which can make marked improvement in a patient's memory and quality of life.

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# DEMENTIA STUDY-PROFORMA

NAME: AGE: SEX:

ADDRESS:

## PRESENTING COMPLAINTS:

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1) memory loss duration(months):
2) parasthesia: Y/N
3) anorexia: Y/N
4) skin blackening: Y/N
5) muscle weakness: Y/N
6) Ataxia: Y/N
7) Vision problem: Y/N
8) Psychiatric symptoms: Y/N
9) Diarrhea: Y/N

## PAST AND TREATMENT HISTORY:

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1) Diabetes mellitus: Y/N. Duration:
2) Hypertension : Y/N. Duration :
3) IHD: Y/N. Duration:
4) Dyslipidemia: Y/N
5) CVA in past: Y/N
6) Significant drug history:

7) Smoking:

8) Alcohol:

9) Diet: veg/ non-veg

10) GI surgery:

## ON EXAMINATION:

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1) pallor: Y/N

2) glossitis: Y/N

3) pedal edema: Y/N

4) skin hyperpigmentation:

5) RS:

6) CVS:

7) P/A:

8) CNS: optic neuritis/ atrophy:

Peripheral neuropathy:

Myelopathy:

Hemiplegia:

UMN facial palsy:

Plantar:

Ataxia/ post column signs:

Cerebellar signs:

Pyramidal signs:

9) **DSM-IV CRITERIA:**

major impairment in learning and memory as well as at least one of the following:

- Impairment in handling complex tasks.
- Impairment in reasoning ability.
- Impaired spatial ability and orientation
- Impaired language.

- The cognitive symptoms must significantly interfere with the individual's work performance, usual social activities, or relationships with other people.
- This must represent a significant decline from a previous level of functioning.
- The disturbances are of insidious onset and are progressive, based on evidence from the history or serial mental-status examinations.
- Not occurring exclusively during the course of delirium

10**)** **MMSE:**

1) date: (year)(season)(date)(day)(month) - **__/5** points

2) Where are we: (state)(county)(town)(hospital)(floor) - **__/5** points

3) Name three objects: one second to say each. Ask the patient all three after you have said them. Give one point for each correct answer. Then repeat them until he/she learns all three. Maximum score - **__/3** points.

4) Serial 7s, beginning with 100 and counting backward: one point for each correct; stop after five answers. Alternatively, spell WORLD backwards: one point for each letter that is in correct order. Maximum score - __/**5** points.

5) Ask for the three objects repeated above: one point for each correct. Maximum score - __/**3** points

6) Show and ask patient to name a pencil and wrist watch - __/**2** points

7) Repeat the following, "No ifs ands or buts." Allow only one trial - _/**1** point

8) Follow a three stage command, "Take a paper in your right hand, fold it in half, and put it on the floor." Score one point for each task executed. Maximum score - __/**3** points

9) On a blank piece of paper write "close your eyes," and ask the patient to read and do what it says - __/**1** point

10) Give the patient a blank piece of paper and ask him/her to write a sentence. The sentence must contain a noun and verb and be sensible. Ask him to copy a intersecting pentagon- __/**2** points

**TOTAL MMSE: __/30**

**AFTER TREATMENT (6-8wks):**

MMSE: __/30, anorexia- , parasthesia- , ataxia- , myelopathy- , optic neuropathy- .

**LAB PARAMETERS:**

**1) MCV:**

**2) HB:** **TC:** **PLT:**

**3) PERIPHERAL SMEAR:**

**4) T.B/D.B:** **LDH:**

**5) VITAMIN B12:** **FOLATE:**

**6) TSH:** **T4:** **FTC:**

**7) VDRL:**

**8) HIV ELISA:**

**9) MRI BRAIN/ CT BRAIN:**

**FINAL DIAGNOSIS (CAUSE OF DEMENTIA):**

**LEGEND TO MASTER SHEET:**

**Sex** : 1-male, 2- female

**Dept**: 1- medicine, 2- neurology, 3- geriatrics

**State**: 1- TN, 2- WB, #- Others

**Parasthesia, anorexia, hyperpigm, wkness, imbalance, vision, psych Sx, diarr**: 1-no,2- yes

**Diet**- 1-veg, 2- non veg

**GI Sx, pallor, glossitis, edema, optic neuritis, neuropathy, myelopathy, hemiplegia, bilateral stroke, UMN facial, ataxia, gait, cerebellar**: 0-absent, 1- present

**Plantar**: 1-flexor, 2- extensor

**M1-M10**- MMSE questions 1-10

**M.T**- total MMSE **Maft**- MMSE after treatment

**VDRL, HIV**- 1-non reactive, 2- reactive

**MRI/CT**- 1- normal, 2- cerebral atrophy, 3- multi-infarct state, 4- hippo atrophy, 5-hydroceph, 6- miscellaneous

**Final Dx**- 1-AD, 2- MID, 3- B12 def, 4- unclassified, 5- hypothyroidism, 6- DLBD, 7-NPH, 8-PDD, 9- B12 & MID, 10- B12 & AD, 11- Misc, 12- FTD, 13- Alcohol related, 14- chr meningitis with sequalae, 15- depression.